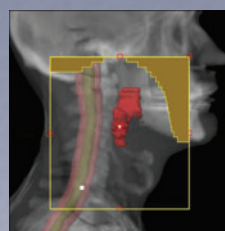
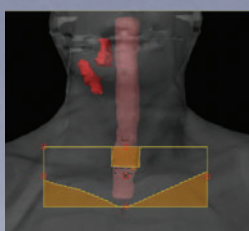
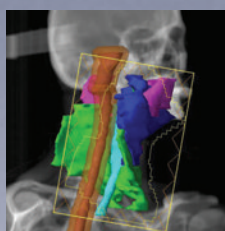
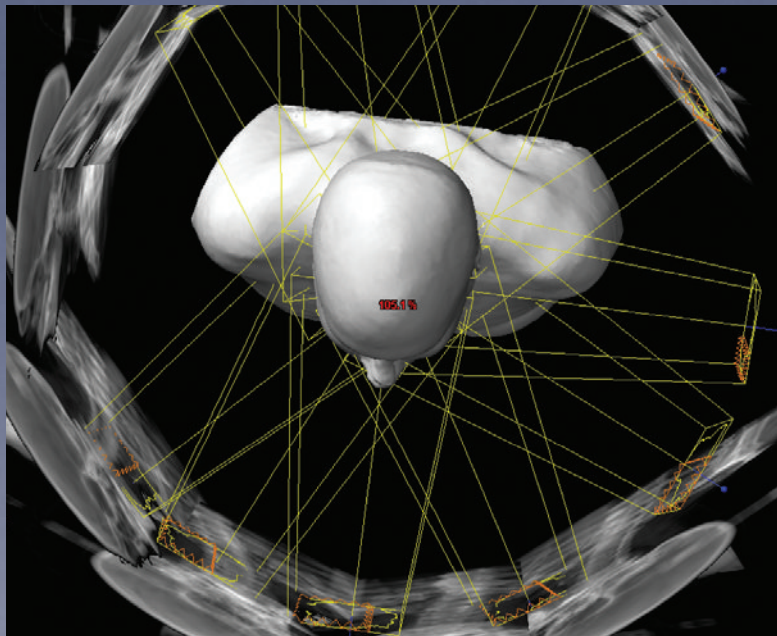


Multidisciplinary Management of Head and Neck Cancer



ROBERT I. HADDAD

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demosMEDICAL
New York

Acquisitions Editor: Richard Winters
Cover Design: Joe Tenerelli
Compositor: S4Carlisle Publishing Services
Printer: Hamilton Printing Company

Visit our website at www.demosmedpub.com

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Library of Congress Cataloging-in-Publication Data

Multidisciplinary management of head and neck cancer / [edited by] Robert I. Haddad.

p. ; cm.

Includes bibliographical references and index.

ISBN 978-1-933864-55-6 (alk. paper)

1. Head—Cancer. 2. Neck—Cancer. I. Haddad, Robert I.

[DNLM: 1. Head and Neck Neoplasms—therapy. 2. Combined Modality Therapy—methods. WE 707]

RC280.H4M825 2011

616.99'491—dc22

2010037088

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Made in the United States of America

10 11 12 13 14 5 4 3 2 1

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Preface

Head and neck cancer affects more than half a million individuals annually around the globe. This is a devastating diagnosis with life changing implications. The treatment of head and neck cancer is highly complicated and involves the use of chemotherapy, radiation therapy, and surgery. The complications associated with the treatment can be quite severe, and many are permanent. There have been significant advances associated with all three modalities over the past two decades, and this has altered our management strategies. Recently, we have also developed a better understanding of the epidemiology associated with the development of oropharynx cancer. This book has been developed with these concepts in mind and will serve as a reference in guiding clinicians in the understanding and management of this disease.

There is a strong focus on treatment strategies with chapters addressing the use of chemotherapy, concurrent chemoradiotherapy, and sequential chemoradiotherapy in this disease. The field of medical oncology is clearly moving toward a personalized treatment approach, and biologic and targeted therapies have become a mainstay in treating head and neck cancer. Chapters 3 and 6 address this important and timely topic.

Radiation therapy has remained an integral and important part in treating these patients, and many advances have been seen recently in this field with the widespread application of intensity-modulated radiation therapy (IMRT). This has resulted in an improvement in patients' quality of life. Chapter 2 is dedicated to review the use of radiation therapy in head and neck cancer.

Surgery is the oldest modality used to treat head and neck cancer and the most feared by patients. The implications on cosmesis, speech, and swallow can be severe. The recent advances in minimally invasive surgery have made their way into head and neck surgical oncology, and the use of robotic surgery is now routine in many institutions. Chapter 5 is dedicated to this topic with a focus on its applications and integration with other treatment modalities.

Infection with the human papillomavirus is now a recognized etiology in the development of oropharynx cancer, and this has significantly altered how we think of oropharynx cancer in particular. Chapter 1 addresses this entity given its relevance in the field.

Other important topics are also covered, such as the use of nuclear imaging in head and neck cancer and advances in nasopharyngeal and thyroid cancers. Finally, Chapter 9 is dedicated to the evaluation and treatment of dysphagia and aspiration in these patients.

All the chapters in this book emphasize multidisciplinary care and integration of the most practical, evidence-based, and up-to-date treatment modalities in treating patients with head and neck cancer. I trust that this volume will be of value to readers, and I hope that the principles detailed here can be applied to achieve better outcomes for our patients.

ROBERT I. HADDAD, MD

Acknowledgments

I would like to thank my patients and their families; your courage is a source of inspiration. I learn so much from you. I would also like to thank my mentors, especially Drs. Marshall Posner and Judith Karp; I am eternally grateful for your guidance and support. I thank my colleagues and friends at the Dana Farber Cancer Institute; your daily and relentless fight against cancer is truly unbelievable.

A special note of thanks to my wonderful parents, Ibrahim and Jeanette; your devotion and encouragement will always guide me. I also thank my two daughters, Kelly Mia and Elsa Maria, who at ages five and three show me every day what is really important in life.

Finally, I dedicate this book to my wonderful wife Pascale whose love, patience, and support keep me going. She is the finest person I know.

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CHAPTER 1

Role of HPV Infections in Head and Neck Cancer

Lisa Licitra, Laura D. Locati, Cristiana Bergamini, and Paolo Bossi

Head and neck squamous cell carcinomas (HNSCCs) arise from the mucosa of the upper digestive tract. Head and neck cancers are subcategorized according to their site of origin due to different etiology, management, and outcome. Strong carcinogenic and epidemiologic evidences support an etiopathogenetic role of tobacco and alcohol; in fact, about 90% of cases are due to them. Recently, oncogenic human papillomaviruses (HPVs) have been associated with a subset of HNSCC (1). HPV DNA (mainly HPV16) is present in the tumor, more frequently in those arising in the oropharynx, although it has also been rarely detected in the oral cavity, larynx, and hypopharynx. HPV-positive testing varies across countries in different series, ranging from 20% to 72%, depending also on the detection techniques (2). In general, more recent studies tend to report an increase in HPV tumor positivity (3). Moreover, a relative rising number of oropharyngeal cancers, together with a declining incidence of oral cavity, larynx, and hypopharyngeal cancer, have been reported in the United States and Europe (4–7). In Sweden, the proportion of HPV-positive tonsillar cancers has significantly increased since the 1970s, with 93% of positivity in 2006–2007, thus suggesting a virus-induced carcinoma epidemic with the virus's presence in virtually all tonsillar cancers, similar to cervical tumor (8).

■ HPV AS ETIOLOGICAL FACTOR

Similar to cervical cancer, high-risk sexual behaviors, HPV exposure, and infection to high-risk viruses have been correlated with oropharyngeal cancer in a case-control study (9).

Sexual behavior increasing the risk of developing HPV oropharyngeal-associated cancer has been defined as having more than 6 lifetime vaginal partners; having oral sex, anal sex, and never or rarely using condoms; and having sexual partners with a history of HPV-related cancers.

When just infection is taken into account, then oral sex and open mouth kissing are associated with an increased probability of oral HPV infection. The infection prevalence has been reported to be low; in a college-aged men's cohort it is 3%, whereas that in a nonselected general outpatient clinic population is 5% (10).

In the HIV-positive population, HPV-related cancers are statistically significantly higher than those in the general population (11). However, in contrast to the high risk of other HPV-associated cancers, the risk of developing oropharyngeal cancer was only statistically modestly increased and, paradoxically, the onset of oropharyngeal tumors was more frequent in AIDS patients with a relatively higher CD4 T-cell count. One explanation

is that not every oropharyngeal cancer is related to HPV infection. Nevertheless, HIV-positive patients treated with active antiretroviral therapy are expected to live longer, thus increasing their risk of developing HPV-related tumors, including oropharyngeal cancer (12). Moreover, there are consistent reports of an increased oral HPV prevalence among individuals on antiretroviral therapy (13,14), highlighting the need to perform studies on the potential benefit of oral cavity screening.

Markers of exposure and infection, such as HPV16 viral capsid (L1) serologic status; HPV16 oral infection; any HPV oral infection, E6 and E7; and HPV16 oncogenes serologic status, have been found to be significantly associated with the risk of developing an oropharyngeal cancer. This risk seems to be independent of alcohol and tobacco use. In particular, in HPV16 seropositive patients the risk was not affected by an increase in alcohol and smoking consumption (15). On the contrary, in seronegative patients this risk significantly increases with increased alcohol intake and smoking. In general, HPV16 seropositivity was associated with a 10-fold increased risk of pharyngeal cancer after adjusting for alcohol and tobacco use. Among patients drinking less than 3 drinks per week or among never-smoker patients, HPV seropositivity was associated with a 30-fold increased risk of developing a pharyngeal cancer.

Interestingly, smoking habits can have a modulating impact on the favorable prognostic outcome of HPV-positive patients, as it has been recently demonstrated (16).

HPV oral infection through serial analysis of oral rinse could also be exploited to detect not only subjects at risk of developing tumors but also to provide earlier evidence of tumor recurrence after therapy. It has been shown that in the majority of cases the HPV variant sequence is of the same type as the index tumor. Its presence has been shown for as long as 5 years. Moreover, the prevalence of high-risk HPV infections other than HPV16 is common in patients with HPV16-positive tumors before and after treatment (17). In some rinses, a different HPV variant was detected, suggesting the possibility of a

different infection. According to this study, no correlation was found between HPV persistence and development of tumor recurrence and/or second tumors. However, numbers were small and follow-up still brief to conclude that this marker is helpful in the clinic. In another small case series, the presence of HPV16 E6 and E7 in convalescent salivary rinses turned out to predict tumor recurrence or metastasis (18). Contrary to cervical infection, the time course of oral infections is still unknown. Similar to cervical cancer, genetic variants such as human leukocyte antigen class I and chemokines may influence viral oral clearance, but individual predisposition of HPV oral infection has to be further investigated. Interestingly, familial clustering of HPV-related cancers, including oropharyngeal tumor site, has been described by the Swedish database. The study could not establish whether the observation was due to shared environmental or genetic factors (19). Genetic susceptibility of developing HPV-related head and neck cancers has been reported to be represented by p53 codon 72 polymorphism and with a variant vitamin C transporter SLC23A2 (20,21).

A biological causal relationship has been postulated on the basis of the integration of HPV DNA, particularly HPV16 and the expression of oncogenic viral genes, such as E6 and E7, and a high viral load that has been consistently found in oropharyngeal carcinomas (22). Indeed, this has been less rigorously demonstrated for other head and neck sites. It is possible that the oropharynx offers a facilitated access to the mucosal basal cell layer in the tonsillar crypts, similar to what happens in the cervical transformation zone. HPV16 is the most common type identified in all head and neck cancers; in less than 10% of cases other high-risk types (18,23–25) have been detected. Corollary evidence is provided by the presence of antibodies directed against HPV16 E6 and E7 oncoproteins, HPV seropositivity, and oral HPV in patients with HPV-positive oropharyngeal cancers.

Molecular alterations, including those occurring at p53, cyclin D1, p16, and pRB, in tumors induced by HPV, are typically different compared with HPV-negative squamous head and neck carcinoma,

supporting the existence of 2 distinct carcinogenetic pathways. The recognized oncoproteins are E6 and E7; however, their expression is not sufficient to cause malignant progression, and the mechanisms by which this happens remain to be elucidated together with the question whether this is common with other HPV-related cancers (26).

Other markers, such as epidermal growth factor receptor (EGFR) expression, have been found to be inversely correlated with HPV positivity (27). Interestingly, hypoxia markers were not found to be correlated with HPV positivity, thus suggesting that this may not be the mechanism responsible for the radiosensitivity of HPV-positive tumors (see later) (28,29). In gene expression analysis, HPV-positive tumors typically display an upregulation of cell cycle regulatory genes (26).

Genetic patterns are also different in head and neck cancer, either containing or lacking transcriptionally active HPV. HPV-positive tumors are characterized by occasional chromosomal loss; on the contrary, in HPV-negative tumor cells there are gross chromosomal deletions typically seen in the early phase of tumor development (30,31). In a recent study, chromosomal alterations among HPV-positive cancer cells of cervical and oropharyngeal origin have been shown to be organ-site specific (32).

■ HPV AS PROGNOSTIC FACTOR

Survival of patients with HPV head and neck tumors has been analyzed in a study meta-analysis, which showed a lower risk of dying (hazard ratio [HR], 0.85) and a lower risk of recurrence (HR, 0.62) in HPV-positive tumors. Interestingly, this seems to be a site-specific effect because, for example, odds ratio was not different among HPV-positive oropharyngeal versus nonoropharyngeal tumors (33). The different reasons for favorable survival outcome have been hypothesized to be intact apoptotic machinery in response to radiation and possibly chemotherapy, absence of field cancerization and immune system activation by viral-specific tumor-associated antigens, and more recently by

radiotherapy or chemotherapy itself (23,34). In addition, among patients with HPV-positive tumors those able to mount serologic immune response against viral E6/E7 have been reported to have a better outcome (34). They are all based on the recognition of a separate and specific biologic profile of HPV-positive tumors that justify its distinct behavior (16,22,35). Interestingly, a better outcome has been seen for patients undergoing primary surgery for oropharyngeal cancer, also suggesting the possibility of a less aggressive tumor (42). Better outcome has been found for the majority of outcome measures, including overall survival, progression-free survival, locoregional control, and second primary tumors (except for distant metastasis) for more than 400 oropharyngeal cancer patients undergoing primary concomitant chemoradiation within a randomized phase III Radiation Therapy Oncology Group (RTOG) study. This trial studied accelerated versus standard fractionation in combination with concurrent 2 or 3 cycles cisplatin, and no effect of HPV/p16 positivity was detected (16,34), confirming that treatment intensification might be useless especially in HPV-positive oropharyngeal tumors. Interestingly despite better outcome, initial studies reported a trend toward a more advanced N stage among HPV-positive tumors. This was recently confirmed together with a more advanced T stage (35) possibly affecting the risk of developing distant metastasis.

Prospective studies including HPV-positive tumors also showed a statistical improvement in response rates as well as organ preservation data, disease-free survival, and better survival (36,37). One of these studies pointed out that the response rate to induction chemotherapy correlates with HPV16 gene copies quantified in the single tumor. The same observation was done by considering p16 tumor staining, which is now recognized as an effective and reliable marker of HPV positivity in head and neck cancer (16–35,41).

Indeed, p16 immunohistochemical expression has been strongly correlated with *in situ* hybridization and HPV gene expression through polymerase chain reaction analysis (16–38).

Smoking status, categorized as never smoker, past smoker, and current smoker, has been associated with the outcome in patients with HPV-positive oropharyngeal cancer (16,39). For some still unclear reasons, current and past smoking negatively affects the cure rates of HPV-positive tumors. An inverse correlation between EGFR expression and smoking has also been observed, possibly suggesting a role of the EGFR pathway in determining prognosis. To date, studies that correlate HPV positivity and tumor response to EGFR inhibitors have not been reported. Given the absence of any correlation between EGFR status and tumor response to cetuximab (40), if HPV positivity is associated with a better outcome with EGFR inhibitors, then the reason should not be attributed to the more preserved EGFR status correlated with tumor HPV infection.

■ CONCLUSION

HPV-related head and neck cancer displays an epidemiologic, biological, and outcome profile that has paved the way for considering it as a separate tumor entity that deserves special attention and also special care in the future. The research strategies for HPV-positive tumors are now concentrated in prospectively studying whether a treatment de-escalation to avoid unnecessary acute and late toxicity is foreseeable, for example, by reducing radiation both in terms of total dose and irradiation volumes, by skipping concomitant chemotherapy, or by using biological therapy instead of chemotherapy. By separating those patients, clinical research in head and neck cancer will have to focus on more aggressive tumors, for which biology will have a prominent role in designing future studies.

It has to be recognized that HPV infection is sexually transmitted and any high-risk sexual behavior is associated with oral HPV infection (9). In this context, strategies of primary prevention to reduce high-risk sexual behaviors among adolescents and the young population must be considered in public health. Vaccination of adolescents and young adults to hasten the reduction of HPV16

prevalence has been claimed, although its efficacy at population level has not yet been demonstrated.

■ REFERENCES

1. Gillison ML. Human papillomavirus-associated head and neck cancer is a distinct epidemiologic, clinical, and molecular entity. *Semin Oncol.* 2004;31:744–754.
2. Kreimer AR, Clifford GM, Boyle P, Franceschi S. Human papillomavirus types in head and neck squamous cell carcinomas worldwide: a systematic review. *Cancer Epidemiol Biomarkers Prev.* 2005;14:467–475.
3. Ernster JA, Sciotto CG, O'Brien MM, et al. Rising incidence of oropharyngeal cancer and the role of oncogenic human papilloma virus. *Laryngoscope.* 2007;117:2115–2128.
4. Carvalho AL, Nishimoto IN, Califano JA, Kowalski LP. Trends in incidence and prognosis for head and neck cancer in the United States: a site-specific analysis of the SEER database. *Int J Cancer.* 2005;114:806–816.
5. Shiboski CH, Schmidt BL, Jordan RC. Tongue and tonsil carcinoma: increasing trends in the U.S. population ages 20–44 years. *Cancer.* 2005;103:1843–1849.
6. Licitra L, Zigon G, Gatta G, et al. Human papillomavirus in HNSCC: a European epidemiologic perspective. *Hematol Oncol Clin North Am.* 2008;22:1143–1153.
7. Chaturvedi AK, Engels EA, Anderson WF, Gillison ML. Incidence trends for human papillomavirus-related and -unrelated oral squamous cell carcinomas in the United States. *J Clin Oncol.* 2008;26:612–619.
8. Nasman A, Attner P, Hammarstedt L, et al. Incidence of human papillomavirus (HPV) positive tonsillar carcinoma in Stockholm, Sweden: an epidemic of viral-induced carcinoma? *Int J Cancer.* 2009;125:362–366.
9. D'Souza G, Kreimer AR, Viscidi R, et al. Case-control study of human papillomavirus and oropharyngeal cancer. *N Engl J Med.* 2007;356:1944–1956.
10. D'Souza G, Agrawal Y, Halpern J, et al. Oral sexual behaviors associated with prevalent oral human papillomavirus infection. *J Infect Dis.* 2009;199:1263–1269.
11. Chaturvedi AK, Madeleine MM, Biggar RJ, Engels EA. Risk of human papillomavirus-associated cancers among persons with AIDS. *J Natl Cancer Inst.* 2009;101:1120–1130.
12. Gillison ML. Oropharyngeal cancer: a potential consequence of concomitant HPV and HIV infection. *Curr Opin Oncol.* 2009;21:439–444.

13. D'Souza G, Fakhry D, Sugar EA, et al. Six-month natural history of oral versus cervical human papillomavirus infection. *Int J Cancer*. 2007;121(1):143–150.
14. Cameron JE, Mercante D, O'Brien M, et al. The impact of high active antiretroviral therapy and immunodeficiency on human papillomavirus infection of the oral cavity of human immunodeficiency virus-seropositive adults. *Sex Transm Dis*. 2005;32(11):703–709.
15. Applebaum KM, Furniss CS, Zeka A, et al. Lack of association of alcohol and tobacco with HPV16-associated head and neck cancer. *J Natl Cancer Inst*. 2007;99:1801–1810.
16. Gillison ML, Harris J, Westra W, et al. Survival outcomes by tumor human papillomavirus (HPV) status in stage III–IV oropharyngeal cancer (OPC) in RTOG 0129. *J Clin Oncol*. 2009;27(15S):301s.
17. Agrawal Y, Koch WM, Xiao W, et al. Oral human papillomavirus infection before and after treatment for human papillomavirus 16-positive and human papillomavirus 16-negative head and neck squamous cell carcinoma. *Clin Cancer Res*. 2008;14:7143–7150.
18. Chuang AY, Chuang TC, Chang S, et al. Presence of HPV DNA in convalescent salivary rinses is an adverse prognostic marker in head and neck squamous cell carcinoma. *Oral Oncol*. 2008;44:915–919.
19. Hussain SK, Sundquist J, Hemminki K. Familial clustering of cancer at human papillomavirus-associated sites according to the Swedish Family-Cancer Database. *Int J Cancer*. 2008;122:1873–1878.
20. Ji X, Neumann AS, Sturgis EM, et al. p53 codon 72 polymorphism associated with risk of human papillomavirus-associated squamous cell carcinoma of the oropharynx in never-smokers. *Carcinogenesis*. 2008;29:875–879.
21. Chen AA, Marsit CJ, Christensen BC, et al. Genetic variation in the vitamin C transporter, SLC23A2, modifies the risk of HPV16-associated head and neck cancer. *Carcinogenesis*. 2009;30:977–981.
22. Vidal L, Gillison ML. Human papillomavirus in HNSCC: recognition of a distinct disease type. *Hematol Oncol Clin North Am*. 2008;22:1125–1142, vii.
23. Vu HL, Sikora AG, Fu S, Kao J. HPV-induced oropharyngeal cancer, immune response and response to therapy. *Cancer Lett*. 2010;288(2):149–155. (Epub ahead of print July 21 2009)
24. Smith EM, Pawlita M, Rubenstein LM, et al. Risk factors and survival by HPV-16 E6 and E7 antibody status in human papillomavirus positive head and neck cancer. *Int J cancer*. 2010;127(1):111–117. 2009 Oct. 28 (Epub. ahead of print).
25. Ang K, Pajak T, Rosenthal DI, et al. A phase III trial to compare standard versus accelerated fractionation in combination with concurrent cisplatin for head and neck carcinomas (RTOG 0129): report of compliance and toxicity. Presented at: 49th Annual Meeting of the American Society for Therapeutic Radiology and Oncology; October 28–November 1 2007; Los Angeles, CA.
26. Chung CH, Gillison ML. Human papillomavirus in head and neck cancer: its role in pathogenesis and clinical Implications. *Clin Cancer Res*. 2009;15(22):6758–6762.
27. Perrone F, Suardi S, Pastore E, et al. Molecular and cytogenetic subgroups of oropharyngeal squamous cell carcinoma. *Clin Cancer Res*. 2006;12:6643–6651.
28. Kong CS, Narasimhan B, Cao H, et al. The relationship between human papillomavirus status and other molecular prognostic markers in head and neck squamous cell carcinomas. *Int J Radiat Oncol Biol Phys*. 2009;74:553–561.
29. Lassen P, Eriksen JG, Hamilton-Dutoit S, et al. HPV-associated p16-expression and response to hypoxic modification of radiotherapy in head and neck cancer. *Radiother. Oncol*. 2010;94(1):30–35. (Epub. Ahead of print November 10)
30. Braakhuis BJ, Snijders PJ, Keune WJ, et al. Genetic patterns in head and neck cancers that contain or lack transcriptionally active human papillomavirus. *J Natl Cancer Inst*. 2004;96:998–1006.
31. Klussmann JP, Mooren JJ, Lehnen M, et al. Genetic signatures of HPV-related and unrelated oropharyngeal carcinoma and their prognostic implications. *Clin Cancer Res*. 2009;15:1779–1786.
32. Wilting SM, Smeets SJ, Snijders PJ, et al. Genomic profiling identifies common HPV-associated chromosomal alterations in squamous cell carcinomas of cervix and head and neck. *BMC Med Genomics*. 2009;2:32.
33. Ragin CC, Taioli E. Survival of squamous cell carcinoma of the head and neck in relation to human papillomavirus infection: review and meta-analysis. *Int J Cancer*. 2007;121:1813–1820.
34. Spanos WC, Nowicki P, Lee DW, et al. Immune response during therapy with cisplatin or radiation for human papillomavirus-related head and neck cancer. *Arch Otolaryngol Head and neck Surg*. 2009 Nov;135(11):1137–1146.
35. Rischin D, Young R, Fisher R, et al. Prognostic significance of HPV and p16 status in patients with oropharyngeal cancer treated on a large international phase III trial [abstract 6004]. *J Clin Oncol*. 2009; 27(suppl):15s.

36. Fakhry C, Westra WH, Li S, et al. Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. *J Natl Cancer Inst.* 2008;100:261–269.
37. Worden FP, Kumar B, Lee JS, et al. Chemoselection as a strategy for organ preservation in advanced oropharynx cancer: response and survival positively associated with HPV16 copy number. *J Clin Oncol.* 2008;26:3138–3146.
38. Kumar B, Cordell KG, Lee JS, et al. EGFR, p16, HPV Titer, Bcl-xL and p53, sex, and smoking as indicators of response to therapy and survival in oropharyngeal cancer. *J Clin Oncol.* 2008;26:3128–3137.
39. Rischin D, Young R, Fisher R, et al. Prognostic significance of HPV and p16 status in patients with oropharyngeal cancer treated on a large international phase III trial. *J Clin Oncol.* 2009;27(15S):302s.
40. Licitra L, Rolland F, Bokemeyer C, et al. Biomarker potential of EGFR gene copy number by FISH in the phase III EXTREME study: platinum-based CT plus cetuximab in first-line R/M SCCHN. *J Clin Oncol.* 2009;27(15S):302s.
41. Lassen P, Eriksen JG, Hamilton-Dutoit S, et al. Effect of HPV-associated p16INK4A expression on response to radiotherapy and survival in squamous cell carcinoma of the head and neck. *J Clin Oncol.* 2009;27:1992–1998.
42. Licitra L, Perrone F, Bossi P, et al. High-risk human papillomavirus affects prognosis in patients with surgically treated oropharyngeal squamous cell carcinoma. *J Clin Oncol.* 2006;24:5630–5636.

CHAPTER 2

State of the Art in Radiation Oncology in the Multidisciplinary Treatment of Head and Neck Cancer

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■ INTRODUCTION

Radiation therapy is the core component of non-surgical treatment of squamous cell cancer of the head and neck (SCCHN). Treatment of this anatomic region represents a significant early use of radiation therapy and remains one of the most critical areas in which external beam radiation is used. Surgery was the earliest definitive therapy for SCCHN and is still an important treatment option, frequently used in combination with radiotherapy. Whether used as initial therapy in a patient who may ultimately require postoperative radiotherapy or as an adjuvant for a postradiotherapy neck dissection, there is a strong history of these 2 modalities being used together. In contrast, current treatment protocols have a steadily increasing role for systemic therapy delivered both with and prior to definitive radiation therapy. Thus, radiotherapy occupies a central position in the modern, multimodality curative treatment of SCCHN. This disease site can thus serve as a model for how to practice combined modality therapy to achieve optimal patient outcomes.

The treatment of SCCHN is one of the most challenging and complex areas within the field of radiation oncology. The anatomy of the head and

neck is complicated, with multiple target sites, including gross tumor, adjacent areas at high risk for microscopic disease, and prophylactic lymph node regions, all requiring treatment to different doses. These tumor-related targets are intertwined with critical radiation-sensitive normal tissue structures whose functioning is essential to many day-to-day activities, including chewing, swallowing, and speaking. As a consequence of the anatomic and treatment complexity of this region, head and neck radiation therapy is a discipline within radiation oncology that can take advantage of many of the available technological advances. These new advances allow us to achieve increased tumor control, but the increased treatment intensity may be associated with increased toxicity. This chapter addresses these innovations, the best way to implement them, and the interaction of radiation oncology with other specialties for head and neck treatment.

Specific Topics

Practice of Radiation Therapy

Our initial focus is on the actual delivery of radiation therapy to the patient. This discussion

includes the following: How to best prepare and position the patient to receive this therapy, how to incorporate diagnostic information in the treatment plan, and the many improvements in accurately delivering a specified dose distribution to the patient.

Setup/Immobilization/Monitoring

Arranging and verifying that the patient is in a stable, reproducible position is the essential first step in delivering precision radiation treatment. This is a fundamental process, but fraught with potential complications for head and neck treatment, where the anatomy allows for multiple degrees of freedom. Stable immobilization devices, image-guided adjustment techniques, and complex verification algorithms are critical. If position changes from the original simulated setup are detected, the detailed image/setup verification techniques can aid in making appropriate adjustments.

Target Delineation

Determining the boundaries of the targets to be treated is the next step in preparation for delivery of radiation. This part of the treatment process is heavily influenced by technological advances in imaging. Delineating the target is, however, more than just translating pixel-to-pixel data. This is particularly true in SCCHN, where evaluation and physical examination are critical to determining the full extent of the tumor. Actual delineation of targets also incorporates the physician's knowledge of the natural history of the disease and pathways of spread. These factors have always been important in treating SCCHN, but the availability of new imaging techniques greatly enhances our base of information. In addition, the need to identify targets on axial images increases the importance of detailed knowledge of disease distribution. Furthermore, the imaging can be a powerful tool for following changes in the tumor size/shape before or during treatment.

Treatment Delivery/Dose Calculation

This is the area of radiation therapy in which the most significant advances have been made. The

ultimate goal of many of the new technologies is to improve the physical dose distribution of treatment. A principal component of this improvement is the development of different methods for delivering the dose. Intensity-modulated radiation therapy (IMRT) is perhaps the most widely known new technology, but the advances also include axial delivery of dose (volumetric arc radiation therapy, tomotherapy) and the use of distinct types of radiation particles such as protons or neutrons in addition to standard photon therapy. Another aspect of IMRT is the new planning technique, which includes inverse treatment planning, where final goals of treatment are specified at the start of the planning process and computer algorithms are designed to construct a plan that achieves these goals. This process has also allowed another practical change: different doses can simultaneously be specified for delivery to different structures, and a single plan can be used throughout the course of treatment. This delivery of differential doses is also referred to as "dose painting."

Fractionation/Timing of Delivery of Radiation

There has been intensive investigation within the radiation oncology community, particularly within the area of SCCHN, to determine the optimal timing and size of each dose to deliver an overall course of radiation therapy (fractionation). Fractionation studies have identified optimal methods for delivering radiation alone in the treatment of SCCHN. Integrating the data from these classic single-modality radiotherapy studies with the new treatment techniques has raised many vexing questions. Unfortunately, up to this point, not many definitive answers have been obtained. One outstanding issue is whether we need to repeat these fractionation studies with the current technology. Many unresolved issues remain about how to alter IMRT with respect to fractionation. There are also new opportunities related to fractionation that take advantage of the improved precision of dose delivery. This technology allows for the possibility of treating head and neck sites with the delivery of a high dose and small number

of fractions treatment in certain clinical situations. This approach is similar to stereotactic radiosurgery (SRS) used for brain treatment and the newly emerging area of stereotactic body radiotherapy (SBRT), which allows this type of fractionation to be used in noncentral nervous system (CNS) sites.

Interaction of Radiation Delivery With Other Modalities

Therapeutic Issues

The interaction between radiation treatment and the other therapeutic modalities, particularly chemotherapy, is an essential factor to consider. Treatment must be addressed as an integrated endeavor and cannot be looked at in isolation for each modality. For example, concurrent or sequential systemic therapy can have a huge impact on a range of radiotherapy parameters. From a wide range of studies, we “know” that concurrent systemic therapy and radiation yield improved outcomes relative to radiation alone. What we do not know is should the use of both agents lead to alterations in the radiation dose or dose distribution that should be delivered to a specified site? It is readily apparent that for concurrent treatment, the IMRT target volumes should stay the same, but in a situation where induction chemotherapy is delivered, the question of how to address these volumes remains an open one. Answering this question is a critical area in the overall treatment approach of using induction chemotherapy as definitive initial therapy for SCCHN patients.

Toxicity

Along with the known oncologic benefits of concurrent chemoradiotherapy, there are strong data demonstrating a parallel increase in the locoregional toxicity with combined modality therapy. This issue has been known for years, but has been exacerbated by the use of new techniques, some of which have a higher intrinsic toxicity than prior methods of delivering radiation. These additional toxicities need to be addressed and then balanced

with any potential benefits from the planned combination therapy. Although there is a great deal of activity within the radiation oncology community to address the radiation-alone toxicities, there still remain limited data for the combination of the new radiation delivery methods and concurrent systemic treatment.

■ TECHNICAL ASPECTS OF RADIATION THERAPY: TARGET DELINEATION/IMAGING

Jonas Salk once commented that “This is perhaps the most beautiful time in human history; it is really pregnant with all kinds of creative possibilities made possible by science and technology which now constitute the slave of man—if man is not enslaved by it.” Salk’s insightful observation has direct implications for head and neck radiotherapy, as an examination of the field’s recent progress and developments reveal vast potential to improve treatment outcomes, but also significant pitfalls of which all practitioners need to be aware.

Brief History of Conformal Radiotherapy

In the early era of radiotherapy, radiation planning was based on external anatomic landmarks and simple measurements of patient thickness (1). These plans were obviously crude, but could be quite effective. The large field size presumably made up for inaccuracies in defining target location. By the 1960s, fluoroscopic simulators, which emulated treatment machine geometry, were developed commercially, allowing radiation oncologists to design fields based on bony anatomy. Radiation planning was performed in 2 dimensions following the fluoroscopic simulation, in which plain radiographs were taken in the treatment position. The external contour of the patient was modeled at the isocenter of the field, and relevant internal structures were drawn on the contour by the physician, including the target and critical normal organs.

The location of these structures was determined by their relationship to bony anatomy. The radiation plan was then devised on this contour; occasionally other contours were taken above or below the isocenter if the patient's thickness varied substantially (2). Although the visualization of bony anatomy allowed radiation fields to become more complex, they were still fundamentally limited by an inability to know the three-dimensional (3D) location of the tumor and surrounding normal structures.

The 1970s witnessed the dawn of axial imaging, as computed tomography (CT) and magnetic resonance imaging (MRI) were developed and introduced into medical care (1). As physicians were then able to incorporate their understanding of a patient's anatomy into the fluoroscopic planning, the importance of having a standard nomenclature for tumor volumes and normal structures became clear.

In 1978, the International Commission on Radiation Units and Measurements (ICRU) issued Report 29, which was its first attempt to define standard volumes for radiation treatment planning (3). Three volumes were defined: the *target volume*, which was the volume containing tissues that were meant to be irradiated to the prescribed dose, the *treatment volume*, which was the volume actually contained by the prescribed dose, and the *irradiated volume*, which was the volume enclosed by a dose considered significant to normal structures. ICRU 29 also defined a *hot spot* if an isodose line above 100% of the target dose included an area at least 2 cm² in a cross section. Finally, an *organ at risk* (OAR) was defined as a particularly radiosensitive organ near the target volume that influenced treatment planning. These definitions provided a vocabulary with which radiation oncologists could report radiation dosimetry and its relationship to outcomes and toxicity. However, the planning itself was still based on hand-drawn volumes extrapolated from medical imaging.

With the development of CT, it became obvious to radiation oncologists and physicists that the technology could revolutionize radiation

planning (4). First, the anatomic detail dramatically improved the physician's knowledge of tumor extent, and theoretically this information would lead to better target coverage. Second, the 3D data set would allow the radiation planner to create a substantially more sophisticated beam arrangement, using computerized dosimetry and a "beam's eye view" to optimally cover the tumor and avoid normal structures (5). Multiple research groups attempted to merge CT technology with radiotherapy planning, and by 1996, several commercial 3D planning systems became available, bringing conformal radiotherapy into general practice (6). Radiotherapy plans created by these systems are termed 3D-conformal radiotherapy (3D-CRT), in contrast to the plans calculated from fluoroscopic simulators, simply termed two dimensional (2D).

The evolution of radiotherapy planning from a process based on bony anatomy to one based on soft tissue anatomy necessitated a new paradigm for prescribing and reporting the radiation dose. ICRU Report 50, issued in 1993, clearly defined 3 new volumes that have changed the way radiation oncologists determine their fields and dose. The *gross tumor volume* (GTV) was defined as the volume encompassing all visible tumor. The *clinical target volume* (CTV) was the GTV plus the additional volume, which encompassed microscopic disease invisible to standard imaging (3). Both the GTV and CTV are radiologic and biological concepts that are separate from any issues regarding setup inaccuracy or tumor motion. The *planning target volume* (PTV), in contrast, was defined as the volume used for treatment planning after a margin had been added to the CTV to account for setup error and tumor motion. As opposed to the GTV and CTV, the PTV could be modulated by reducing patient setup errors and tumor movement. ICRU 50 essentially maintained the other definitions of ICRU 29, but it did comment that intrafractional movement of the OAR should be considered in its dose tolerance.

The current era of head and neck radiotherapy was ushered in by the development of IMRT, which is best described as a revolutionary step in treatment

delivery and planning. IMRT will be described in greater detail in the next section. In brief, it is defined by 2 critical features: 1) inverse planning, refers to the physician specifying the minimal and/or maximal dose to a structure, and then complicated algorithm determines the optimal beam arrangement to obtain that dose; and 2) intensity modulation, in which the radiation intensity is rapidly changed across a given field. The combination of these technologies results in radiation plans that are highly conformal around radiation targets. In principle, IMRT can lead to improved outcomes. Doses to critical structures can be minimized while maintaining the same dose to the GTV and CTV, or doses to critical structures can be kept constant and the GTV and CTV doses increased. The advent of 3D-CRT and IMRT has also led to a new and crucial need to optimally define the contours of both tumor and normal tissue. A failure to appropriately delineate volumes could lead to geographic miss or severe toxicity.

Approaches to Improve Tumor Delineation

In the current era of IMRT, it is imperative to explicitly define the volumes of gross tumor (i.e., GTV) and potential microscopic disease (i.e., CTV). The GTV includes both the primary tumor and nodal disease, and there are different challenges inherent in accurately identifying these regions. Whereas the primary tumor is generally visible on CT imaging, determining its exact extent can be extremely difficult; in contrast, gross nodal disease is relatively easy to contour, but subcentimeter positive nodes are virtually impossible to identify on standard CT. The clinical exam will always be a critical part of radiation planning, but many subtleties of tumor extent will require more sophisticated imaging modalities. Radiologic methods to discern regions of cancer from benign tissue fall into 2 general categories: anatomic imaging and functional imaging.

Anatomic Imaging and Construction of Contours

Because CT simulation has become the standard of care in planning head and neck radiotherapy, it

is worthwhile to consider the ability of physicians to reliably and accurately define gross tumor and nodal disease on CT.

An important study evaluating GTV reproducibly was performed by the American College of Radiology Imaging Network (ACRIN), in which 8 experienced physicians (4 radiation oncologists and 4 neuroradiologists) were asked to contour the GTV of 20 patients with supraglottic carcinoma (7,8). Although the absolute volume of gross tumor was highly correlated between these clinicians (intraclass correlation coefficient was 0.81), the actual drawn contours were quite different, as the average proportion of overlap was only 0.532. This disagreement in tumor shape may have few clinical ramifications in a classical 2D head and neck field, but IMRT plans based on these volumes could look totally different.

Similar findings were reported by Hoorweg et al, who performed a study in which 3 experienced physicians (2 radiologists, 1 otolaryngologist) retrospectively analyzed pretreatment neck CT of 59 patients with larynx cancer and recorded tumor volume, local cartilage invasion, extralaryngeal extent of disease, cartilaginous sclerosis, and tumor localization of different subsites (9). There was substantial disagreement among these readers, with pairwise k values ranging between 0.34 and 0.73 for total tumor volume and 0.03–0.60 for defining which subsites were involved. These data are concerning that standard CT imaging is insufficient to appropriately define GTVs.

Magnetic resonance imaging offers vastly improved soft tissue definition, and thus attempts have been made to integrate MRI into head and neck treatment planning. Preliminary studies have suggested that MRI improves target delineation in nasopharyngeal cancer, in which brain invasion can be missed by CT. For example, Chung et al showed that nasopharyngeal intracranial extension as shown by MRI was missed by conventional CT in 40% of patients (10). Unfortunately, there was no pathologic confirmation of these findings, which would be preferred to prove that one modality is superior to another. A provocative study from

Taiwan found that nasopharyngeal patients with cranial neuropathies who were staged with MRI had improved local control and survival rates after radiotherapy than patients who did not undergo MRI, suggesting a potentially critical benefit of MRI-based contouring (11).

Other investigators have shown that contouring on MRI results in smaller GTV volumes and more consistency in contouring the GTV. For example, physicians from the Netherlands Cancer Institute compared the GTVs of 6 patients that were contoured by 4 experienced physicians (12). Volumes defined on MRI were smaller (mean CT volumes 1.3 times larger than mean MRI volume) and overlapped a higher percentage of the time than tumor contoured on CT. Similarly, Gardner et al compared the interobserver variation of volumes contoured on MRI and CT, finding that the variation was greater on CT for both normal structures (i.e., parotid) and gross tumor (13). However, without an evaluation of pathologic specimens, it is difficult to know whether this increased consistency represents an improved anatomic delineation of disease. This latter point is well illustrated by a study by Daisne et al in which the investigators compared pathologic findings from 9 laryngectomy specimens to contours based on CT, MRI, and fluoro 2-deoxyglucose-positron emission tomography (FDG-PET) imaging, showing that all modalities underestimated superficial tumor extension onto the contralateral larynx or subglottis as well as extralaryngeal extension (14).

With respect to nodal disease, the sensitivity and specificity CT and MRI are generally thought to be greater than 75% in surgical series with preoperative imaging, but some studies have suggested sensitivities and specificities as low as 50% (15–18). Both imaging techniques appear equally capable of identifying extranodal extension, although this question has been less well studied (19). Unfortunately, the definition of a positive node was heterogeneous throughout all of these studies, and the impact of this varying definition cannot be underestimated; Curtin et al showed that different size and morphology criteria

for positivity can change the diagnostic performance of both CT and MRI by more than 30% (20).

Although both CT and MRI have their strengths as imaging techniques for radiation planning, there is clearly room for improvement, and the drive for more precise tumor definition has led radiation oncologists to investigate biological imaging.

Biological Imaging

Although anatomic detail is important in distinguishing tumor from normal tissue, the development of molecular imaging offers the potential to directly visualize malignant processes and thus incorporate them into radiation planning. The most commonly used (and studied) functional technique is positron emission tomography (PET), which is a nuclear medicine study in which a positron-emitting isotope is attached to a molecule relevant to tumor activity. The addition of correlative CT imaging in the same machine, termed positron emission tomography-computed tomography (PET-CT), has improved the sensitivity and specificity of the modality (21).

The most commonly used isotope is the glucose analog 18-fluorodeoxyglucose (FDG), which is preferentially taken up by tumor cells relative to normal tissue (22).

Given the difficulty in tumor definition using CT alone, PET-CT has been investigated as a tool to further refine GTVs. Several studies comparing FDG-PET-based planning with standard CT simulation have been published, and most of these studies have shown a significant decrease in the total GTV volume by using PET-based contouring (23). There is also compelling evidence that there is less variation in GTV contours among physicians when incorporating PET-CT imaging; Ashamalla et al compared the PET-CT-derived and CT-derived tumor volumes contoured by 2 radiation oncologists, finding that the volume of disagreement shrunk from 20.3 cm³ in CT-based contours to 7.2 cm³ with PET-CT-based contours (24).

FDG-PET also has shown promise in identifying positive nodal disease, which should be contoured as GTV. In studies of patients with all

stages of disease who went on to neck dissection, PET appears to have a sensitivity more than 80% and a specificity more than 90% in detecting nodal disease, and in those studies that compared PET to CT alone, PET almost always showed superior accuracy (25–27). However, when the patient cohort included only clinically node-negative necks, the sensitivity of PET dropped substantially, ranging from 25% to 67%, with the specificity ranging from 87% to 98% (28–30).

With such variability in results, it is critical to note several fundamental problems with using PET to guide radiation treatment contours. First, the threshold used to define “positive tissue” from “negative tissue” is different throughout all of these studies. For instance, one study included any tissue with an absolute standard uptake value (SUV) of 2.5, whereas other studies considered any tissue positive if its SUV uptake was 50% of the maximum value (31,32). Thus, until there are validated studies correlating SUV values (either relative or absolute) with the presence of tumor, it is nearly impossible to know at what point faint positivity becomes a false positive. Indeed, in a study investigating the performance of PET-CT in detecting nodal disease, Schinagl et al showed that different PET segmentation levels (i.e., the threshold at which a lymph node was considered positive) dramatically changed the number of lymph nodes the radiologist would consider positive (33).

The second concern with using PET-based volumes relates to our technological ability to register the PET-CT with the planning CT, since they are performed in different scanners, on different days, and sometimes in different positions. Even with nonrigid deformation algorithms, errors in registration have been shown to range from 3.2 mm to 5.4 mm (34–36). Thus, unless registration errors are included in the treatment volumes (presumably in the PTV expansion), contouring on the PET image overlaid on the simulation CT could lead to a contour that is too large or too small simply due to image misregistration.

In the future, the extent to which radiation oncologists will incorporate PET imaging into their

planning is dependent on its ability to visualize more biological processes than just glycolysis, and the development of different tracers may provide radiation oncologists with new, biologically defined targets. Perhaps the most exciting biological target is identifying areas of hypoxia, which are known to be radio- and chemoresistant; thus, there has been interest in increasing the radiation dose to these areas (23). Two tracers have been evaluated for this purpose in head and neck cancer, 18F-fluoromisonidazole (FMISO) and Cu(II)-diacetyl-bis(N(4)-methylthiosemicarbazone) (Cu-ATSM) (23). However, the one prospective study correlating PET-defined hypoxia with local control did not show a relationship between the two (37). Other groups have shown the dosimetric feasibility of using these imaging studies to dose escalate using IMRT, but no clinical outcomes were described (38–40). Until local control can be predicted by hypoxia imaging agents, the benefit of dose escalation to these areas is purely hypothetical.

Issues With Nodal Delineation

The conventional radiotherapy plan for head and neck cancer has a long history of efficacy for controlling nodal disease. However, with the advent of 3D-CRT and IMRT, it became necessary to explicitly contour nodal levels that would receive specified doses, because otherwise these areas may not receive adequate dose. The challenge then becomes merging nodal level definitions on CT with our collective experience of traditional radiation planning, and the dose it successfully delivered to the neck. At least 7 authors and/or groups have proposed CT definitions of these nodal basins, and they disagree, in part because some drew on the surgical experience for defining the neck levels, some on radiographic definitions, and some on both (41–46). This disagreement may have significant ramifications, as shown in an important trial by Sanguinetti et al (46).

This group contoured nodal stations IB-V in 8 N0 or N1 patients according to the nodal

definitions of 7 different authors. Conventional radiotherapy plans were then designed for these patients for 3 different diseases: larynx cancer in which upper, mid, and lower jugular nodes were covered; larynx cancer in which posterior cervical nodes were also covered; and tonsillar cancer, in which retropharyngeal nodes were additionally covered. The dose to the contoured nodal stations was then calculated for each of these conventional plans, and the 50% isodose line—which represents the field edge for conventional lateral beams—was used as the marker for whether the volume was inside or outside of the conventional field. The authors found that neck levels III and IV were adequate for all definitions but that contoured levels Ib, II, and V were often out of the standard field. For instance, up to 21% of the contoured Ib volumes were outside of standard tonsillar fields, raising the question of whether the nodal contours are too generous (or the older fields were too conservative). In addition, on average only 45% of level II and 65% of level V received 95% of the dose delivered from a conventional field. However, conventional radiotherapy did not have a 65% regional failure rate in level V, so the optimal volumes to contour for nodal levels remain a somewhat open question.

Of course, it was imperative to decide on standard nodal definitions to perform multi-institutional trials of 3D-CRT and IMRT. Therefore, several radiation oncologists from the different cooperative groups arrived at a consensus guideline for contouring of the nodal levels, which was a combination of the previously proposed definitions (47). Published in 2003, these guidelines have been adopted by the participating cooperative groups (Radiation Therapy Oncology Group (RTOG), European Organisation for Research and Treatment of Cancer (EORTC), Groupe d'Oncologie Radiotherapie Tete et Cou (GORTEC), National Cancer Institute of Canada (NCIC), and Danish Head and Neck Cancer Group (DAHANCA)) as the gold standard for defining nodal volumes.

Promise of Normal Tissue Sparing With IMRT

As detailed above, intensive efforts have been made to improve the delineation of gross tumor, both in the primary site and nodal basins. The potential benefits of improved target definition are obvious because ensuring all malignant tissue is irradiated to a radical dose should improve local control. Similarly, treating an excessive volume of normal tissue could also lead to untoward outcomes, as the head and neck region contains many critical structures, and damage to any of them could lead to significant morbidity. Prior to 3D-CRT, it was virtually impossible to determine the relationship between dose to normal tissue and late toxicity. However, with the advent of conformal radiotherapy and IMRT, physicians have attempted to determine the radiation tolerances of these crucial organs. Investigators have focused most of their attention on understanding the relationship between radiation dose and long-term xerostomia and dysphagia, and their findings will be briefly described below.

Xerostomia

Xerostomia, or dry mouth, is a symptom that dramatically reduces the quality of life for patients treated with head and neck radiotherapy (48). For instance, in a prospective study of 425 patients treated with head and neck radiation therapy or chemoradiotherapy, 152 developed grade 2 (moderate dryness) xerostomia, and 19 developed grade 3 to 4 (complete dryness/fibrosis) xerostomia (48). The severity of xerostomia was significantly correlated with decreasing quality-of-life scores in several domains, including physical functioning, role functioning, emotional functioning, social functioning, global quality of life, and fatigue. Indeed, since normal salivary production is critical in maintaining taste and dental health in addition to comfort, it is not surprising that xerostomia can profoundly affect quality of life (49).

Since 90% of salivary production is derived from the 3 major salivary glands (parotid, submandibular, and sublingual), the majority of attention has been

focused on the relationship between xerostomia and radiation dose to these structures (49). In a critical early study, Eisbruch et al showed that parotid glands receiving a mean dose less than 26 Gy showed substantial preservation in measured salivary flow after radiotherapy, whereas there was minimal recovery in glands that received a higher mean dose (50). They further supported their findings in a larger cohort of 142 patients treated with either 3D-CRT or IMRT (51). Similar results were published by Jellema et al, who described a significant relationship between xerostomia and sticky saliva and mean parotid and submandibular gland doses. In fact, mean doses to the 2 glands were independently associated with poor salivary outcomes, and there was an interaction term between the two (52). Investigators from the University of Michigan also confirmed that dose to the submandibular glands, which secrete mucins that improve salivary viscosity, correlated with its flow rate after radiotherapy; there was essentially no recovery if the mean dose to the gland was greater than 39 Gy (53).

Ideally, these data could be used to optimally reduce the dose to the parotid and submandibular glands, theoretically reducing long-term xerostomia rates. Preliminary nonrandomized data suggest this is feasible (54,55). Van Rij et al also showed that patients treated with IMRT with a mean parotid dose less than 26 Gy experienced less xerostomia than IMRT-treated patients with a higher mean parotid dose (54). However, as will be shown later, prospective data have raised doubts as to whether subjective xerostomia is truly reduced by more conformal therapy.

Dysphagia

Long-term swallowing dysfunction may be the most debilitating complication from radical radiotherapy. In fact, in a recently reported RTOG study investigating accelerated radiotherapy with concurrent chemotherapy (RTOG 99-14), the gastrostomy tube rate at 1 year was 41%, and it was 17% at 4 years (56). Several studies have shown that gastrostomy dependence significantly reduces multiple quality-of-life domains, including depression, highlighting the need to understand predictors of dysphagia (57,58) Furthermore, in

Langendijk's prospective quality-of-life study following radiotherapy, 11% of patients developed grade 2 dysphagia, and 15% of patients reported grade 3 or 4 dysphagia; there were significant correlations between the degree of dysphagia and each domain of the European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire (EORTC QLQ-C30) (48).

Both clinical and dosimetric factors are associated with long-term swallowing outcomes. For instance, Caudell et al have shown that concurrent chemotherapy, primary site (e.g., larynx, hypopharynx, base of tongue, pharyngeal wall vs. others), and increasing age were all associated with higher rates of dysphagia (59). From a radiotherapy standpoint, however, it is critical to define dosimetric predictors of swallowing dysfunction, as the dose delivered can potentially be altered, but most clinical factors cannot.

In order to understand how radiotherapy may affect swallowing, it is important to understand the actual swallow mechanism. In brief, there are 4 stages of swallowing: oral preparatory, oral, pharyngeal, and esophageal. The oropharyngeal swallow, which is voluntary, includes all events from the lips to the upper esophageal sphincter. After food is chewed and the tongue begins to push the bolus posteriorly, the soft palate moves superiorly to prevent reflux into the nasopharynx, and the posterior pharyngeal wall moves forward. The vocal folds close and the larynx moves superiorly and anteriorly, thus closing the epiglottis and, after the cricopharyngeus muscle relaxes, opening the upper esophageal stricture (60). Damage to any of these structures could potentially impair the swallow mechanism. In fact, the data on dosimetric predictors of dysphagia are wildly conflicting, though the majority of research suggests that dose to the larynx is a consistent predictive factor.

Caglar et al showed that dose to the larynx and inferior constrictors were the only 2 dosimetric parameters significantly associated with both esophageal stricture and aspiration, results echoed by Caudell et al (61,62). For example, in Caglar's study, no patients with a mean dose to the larynx

less than 48.2 Gy developed aspiration. In contrast, a study from the University of Michigan showed that while all pharyngeal constrictors were associated with aspiration, the superior constrictors showed the most consistent relationship (63). These findings were supported by Levendag et al, who also found that dose to the superior and middle constrictors was the most important dosimetric predictor of dysphagia, potentially because of reduced elevation of the larynx during the oropharyngeal swallow (64). And as if only to confuse matters further, Dirix et al reported that mean dose to the supraglottic larynx and middle constrictor muscles were the only significant predictors of worsening QLQ-H&N35 swallowing symptom score, whereas, dose to the superior constrictors or inferior constrictors were not (65).

The significant heterogeneity in these studies makes it impossible to draw definitive conclusions on the optimal dosimetric parameters for these swallowing structures. Different definitions of the dysphagia outcome, as well as a diverse patient population, both with respect to stages of disease, sites of disease, and treatment paradigm, presumably account for a fair amount of these discrepancies. It is clear, though that the region between the epiglottis and cricoid is important to spare from high-dose radiotherapy, and as highly conformal radiotherapy has become the standard of care, appropriately contouring these structures and then avoiding their irradiation takes on a more important role in the outcome.

■ SUMMARY

Radiotherapy as a field has evolved dramatically over the past 20 years, and the potential benefits and risks of the technological innovations are modeled in head and neck radiation therapy. The move toward conformal radiotherapy, and IMRT in particular, highlights the critical new importance of axial imaging and target definition, which is a dramatic shift from bony anatomy-based field design. The next section describes these treatment delivery techniques in greater detail, paying attention to the data that suggest these conformal approaches offer a superior therapeutic ratio.

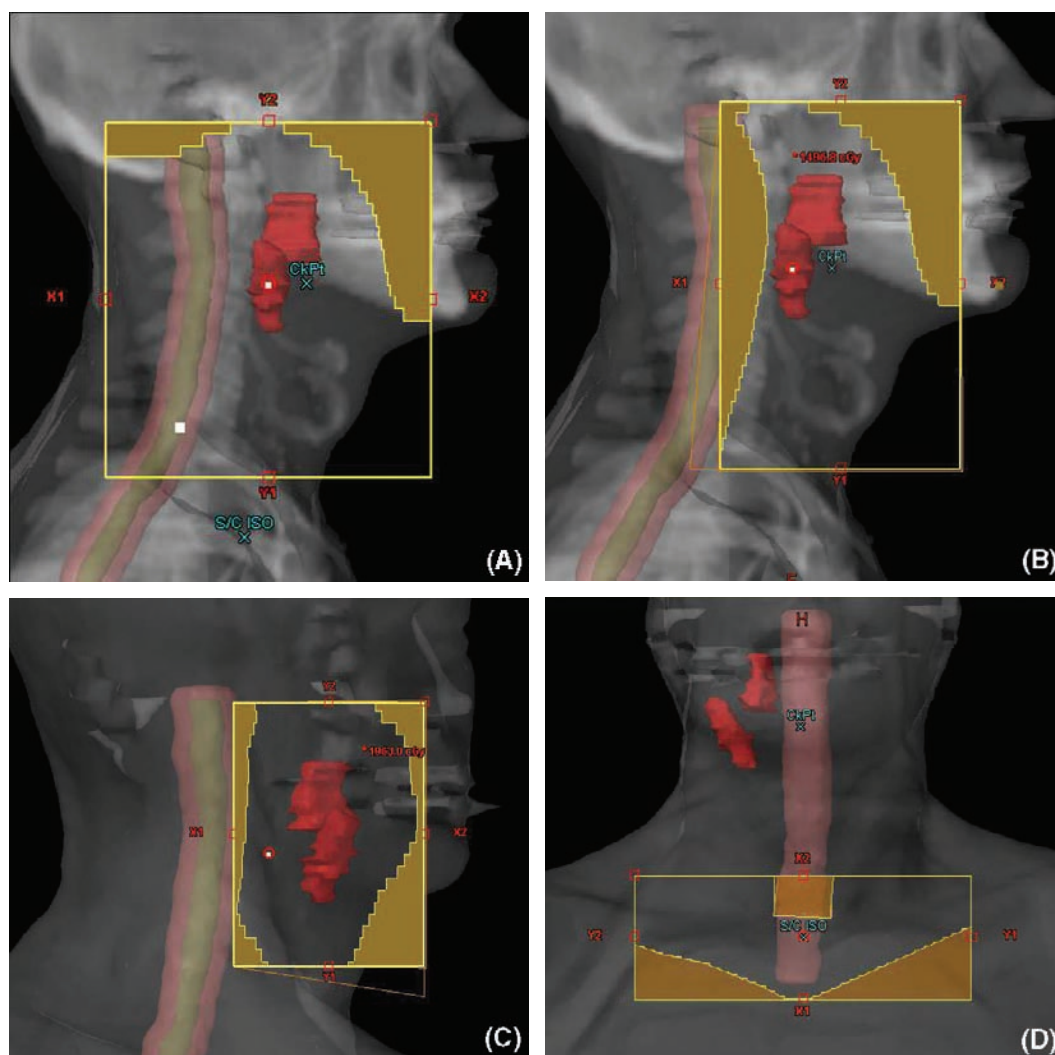
■ TECHNICAL ASPECTS OF RADIATION THERAPY: TREATMENT DELIVERY

Radiation therapy delivery techniques have changed dramatically over the past 20 years, and the current “state-of-the-art” delivery method, IMRT, is virtually unrecognizable from radiotherapy of an earlier era. In order to appreciate the evolution of these techniques, a brief history of head and neck radiation planning is required.

Conventional Head and Neck Radiotherapy

For most of the history of head and neck radiation therapy, the treatment was delivered using a “3-field” plan that was designed using fluoroscopy. This was composed of 2 opposed lateral beams, which treated the primary and nodal gross disease in the upper neck, and an anterior field, termed the “LAN,” or low-anterior neck (6). These fields were matched at either the isocenter—the middle of the field—in which the upper part of the field was delivered as laterals, and the lower part of the field was the LAN, or the inferior lateral and superior LAN fields were matched on skin. A small “cord block” was placed in the LAN at the junction of all 3 fields to limit spinal cord dose and in some cases spare dose to the larynx (Figure 2.1).

Unless there was gross supraclavicular nodal disease, the LAN was treated to approximately 50 Gray (Gy), and then dropped from the daily fields. The opposed laterals were treated to approximately 45 Gy and then broken down into 2 separate fields, a photon beam that was blocked posteriorly to avoid additional dose to the spinal cord, and a matched electron beam that treated the posterior nodal tissue overlying the cord. After an additional dose to the neck and primary region, a final boost, or “cone down,” was applied to regions of gross disease. This process of delivering ever smaller fields was termed the “shrinking-field technique,” and allowed the radiation oncologist to deliver different doses to different volumes of the head and neck (6). Figure 2.1 demonstrates a typical set of progressively smaller fields, used to deliver a 3-field head and neck (HN) treatment.

**FIGURE 2.1**

"Classic" Head and Neck 3-Field Treatment was delivered primarily using lateral opposed fields, matched to a low anterior neck, or supraclavicular, field. The patient is being treated for a T2N2 Tonsil Cancer. All regions included in the fields receive essentially the same dose per day; the fields are shaped by the orange MLC blocks indicated on the films. Initial fields are shown in (A) covering the primary tonsil lesion and lymph node and all lymph node volumes. (B) A "cord block" is introduced, limiting the dose to the more sensitive spinal cord. (C) The final "cone down" is shown, targeting the GTVs. (D) Shows the low anterior neck field. Differential doses are delivered to the different volumes by using a series of "shrinking" fields, obtained by altering the blocks at specific times in the treatment course. The posterior neck was treated with electrons, which have limited tissue penetration. This allows treatment of the more superficial lymph nodes, sparing the underlying spinal cord.

Although this conventional 3-field radiotherapy plan was the standard technique of treating head and neck patients, it delivered a relatively homogeneous dose to the target and was associated with multiple dosimetric limitations. A high dose was unavoidably delivered to the parotid glands and mandible, with a resultant significant risk of xerostomia and osteoradionecrosis. The nontrivial rate of xerostomia has been previously presented, and osteoradionecrosis has been shown to occur in more than 20% of patients whose mandible received a dose 70 Gy or more (66). Additionally, conventional treatment for nasopharynx cancer leads to increased dose to the brain, cochlea, and optic structures, which can result in temporal lobe necrosis, hearing loss, and eye damage, severe consequences of radical radiotherapy to a region draped by critical structures (67–70). Figure 2.2 shows the essentially homogeneous cross-sectional dose distribution resulting from lateral opposed fields.

3D Conformal Radiotherapy

The advent of CT simulation provided radiation oncologists with the ability to design radiation fields that avoided critical structures, such as the parotid. One of the key benefits of 3D planning was the creation of the “beam’s eye view,” which allowed the treatment planner to block normal tissues in the path of a given beam (Figure 2.3).

Radiation oncologists from the University of Michigan performed a dosimetric comparison of 10 2D and 3D head and neck radiotherapy plans, demonstrating that better PTV coverage and lower contralateral parotid dose could be achieved with 3D conformal techniques (71). They followed this publication with clinical data in 15 patients treated with 3D-CRT, showing substantially improved salivary flow in the spared parotid (72). Similarly, in a planning study for nasopharyngeal cancer, Chau et al showed significant improvements in PTV coverage and reduced dose to the brainstem, optic chiasm, and temporal lobes with 3D-CRT in comparison with conventional radiation portal design (73).

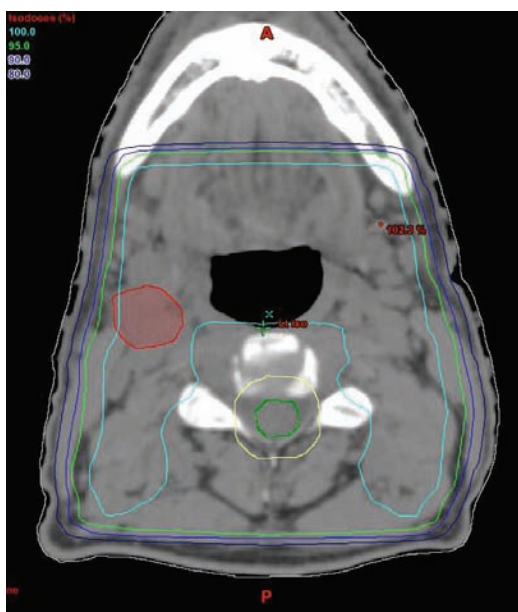


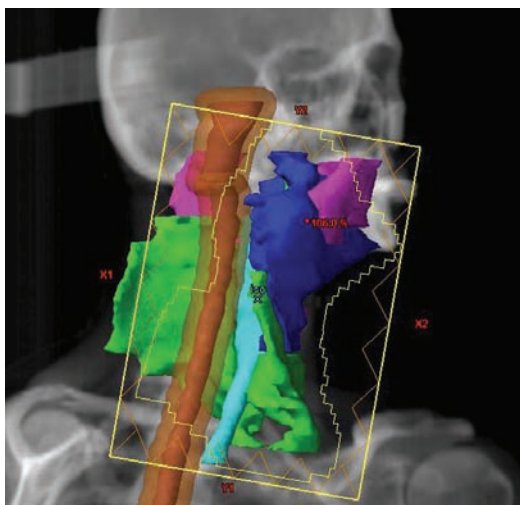
FIGURE 2.2

Axial dose distribution for a 3-field treatment. Typical dose distribution achieved using a field arrangement such as that presented by the lateral fields in Figure 2.1A. The value of the isodose lines are shown in the left upper corner. They range from 100% (light blue) to 80% (darkest blue). Note the relative homogeneity of the doses across the width of the neck.

In actuality, reported clinical outcomes with 3D-CRT are relatively sparse, because the next major research effort quickly focused on IMRT.

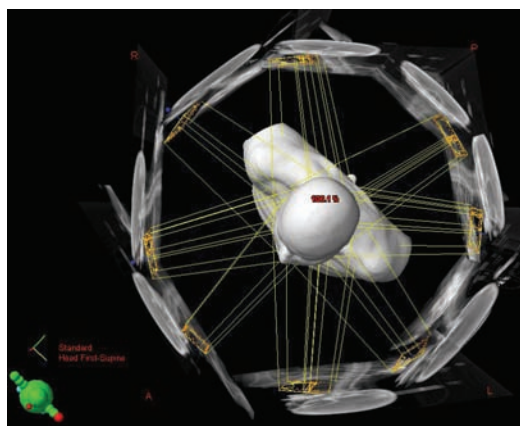
Intensity-Modulated Radiation Therapy (IMRT)

Intensity-modulated radiation therapy employed 2 new concepts in radiation planning and delivery. The first is termed “inverse planning,” in which the physician specifies the dose to tumor volumes (e.g., GTV, CTV, and PTV) and the dose to normal structures (e.g., parotid glands, spinal cord), and the physicist employs a computer algorithm to design a plan to meet those constraints. This process is distinctly different from traditional “forward

**FIGURE 2.3**

"Beam's Eye View" of targets and normal tissues. This image shows what the treatment machine "sees" from a particular angle and illustrates the compromises that need to be made in achieving an optimal dose distribution. At each angle, both normal tissue structures and tumor related targets will overlap. The optimal delivery of dose will be achieved based on a computer algorithm that attempts to achieve dose goals and constraints when the total dose is summed up from the contributions of all different angles. The inner yellow line represents the MLC border. In this example, purple objects represent "avoidance" structures (the parotid glands, the contralateral submandibular gland, the oral cavity, and the larynx). Other normal tissue avoidance structures include: the pharyngeal constrictors/posterior cervical esophagus structure in light blue and spinal cord/brainstem in light brown and expanded volumes in orange. The target structures are the high-risk nodal/primary CTV regions in dark blue and low risk nodal CTV regions in green. Note that the GTVs are within the high risk CTVs and not visible in this 3D rendering.

planning," in which the physician first creates the fields and the physicist or dosimetrist then determines the dose distribution (74). The benefit of the inverse planning algorithm is the ability to carve dose away from multiple normal structures while ensuring a radical dose to the PTV, which is simply too difficult to accomplish with standard planning techniques.

**FIGURE 2.4**

Representation of the multiple fields used for IMRT treatment delivery schematic representation of the fields used to deliver an IMRT plan for head and neck treatment. Note the multiple treatment angles as well as the representation of the field "shapes." In contrast with the static field borders used for 3-field treatment, the borders of the IMRT fields are changing throughout the radiation delivery process. This is carried out by metal leaves termed a multileaf collimator (MLC) moving under computer-guided control. Typically borders for static fields are shaped using nonmoving MLCs or on some machines using actual lead (or cerrobend) blocks.

The second main component of IMRT is, as the name implies, intensity modulation. By definition, intensity is the total energy per unit area per unit time (2). In standard radiotherapy, the intensity across a given beam is basically constant; there is no variation across the field. If a particular beam delivers 100 cGy to a 10×10 cm area at a certain depth, that 100 cm² region is all receiving roughly 100 cGy. In contrast, for a given IMRT field, the intensity throughout the field may vary substantially, a dosimetric feat that is typically accomplished through the use of multileaf collimators (MLCs), narrow moveable leaves in the head of the linear accelerator (4). In IMRT, a given radiation beam is split into multiple subfields, each with a different arrangement of the MLCs, such that the final delivered dose—the summation of each subfield—is highly variable across its area (Figure 2.4 and 2.5).

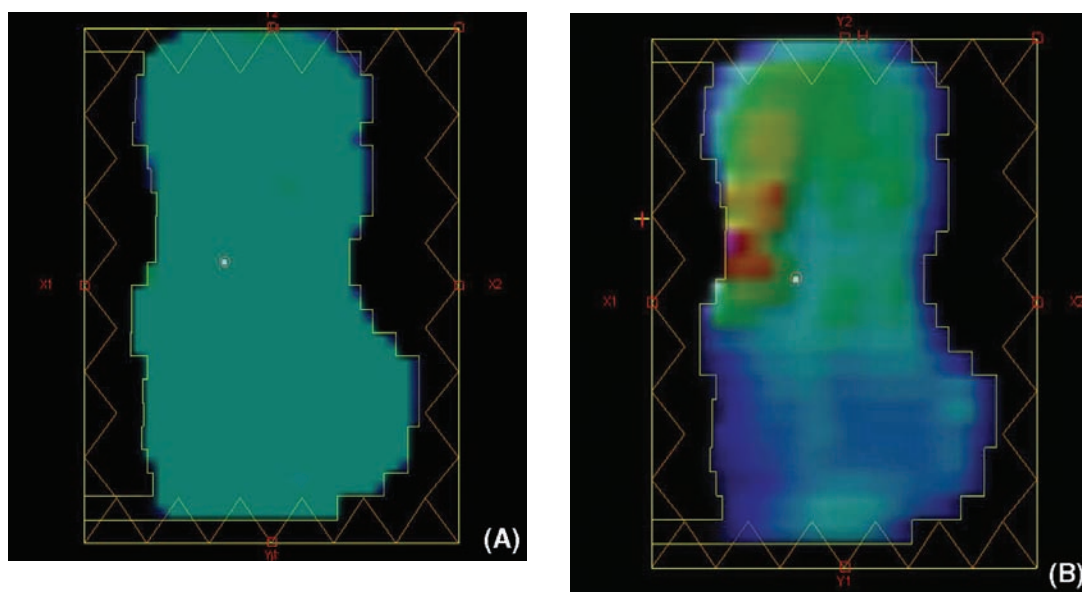


FIGURE 2.5

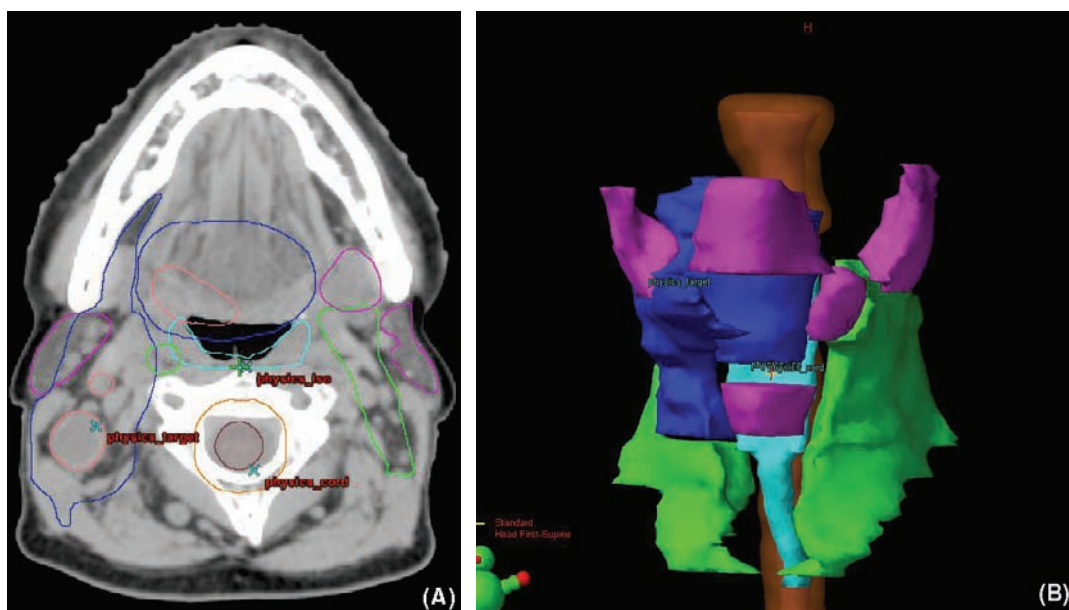
Fluence patterns for standard and IMRT treatment plans. (A) Standard fields with static MLCs or blocks. (B) IMRT field with dynamic MLCs. This is a representation of the beam intensity or “fluence” delivered by a treatment machine for both 3-field and IMRT treatment. In this representation, the reds and oranges correspond to the higher doses, whereas green and blue are relatively lower. The inner yellow line represents the MLC border. In (A) the standard field treatment, the fluence has a fairly homogeneous distribution across the entire field, except for a relative decrease seen at the field edges. In contrast with this, the IMRT fields have a highly variable dose rate across the treated area (B). This is achieved with the dynamic changes in the blocking that results from the MLCs moving during treatment delivery. Courtesy of Dr. Laurence E. Court.

Since different volumes of the treatment field can receive different doses through intensity modulation, a new radiation dosing scheme became feasible—“dose painting,” in which higher risk regions receive a higher daily dose than lower risk regions. For example, in a conventional 3-field design, the low-risk supraclavicular fossa receives approximately 50 Gy through an anterior field delivered over 25 fractions, whereas over the same 25 fractions, the primary disease receives 50 Gy through lateral fields. The anterior field is then discontinued, and the primary disease continues to be treated to the therapeutic dose. In IMRT, the supraclavicular fossa may receive 56 Gy over 35 fractions, at 1.6 Gy per fraction, whereas the gross disease

is given 70 Gy over those same 35 fractions, at 2 Gy per fraction. Thus, the same radiation plan is delivered over the course of treatment, but different PTVs are prescribed different fractional doses. Figure 2.6 demonstrates the target volumes and avoidance structures that need to be contoured prior to constructing an IMRT plan. Figure 2.7 shows a typical IMRT plan and this should be compared and contrasted with the dose distribution seen for 3-field treatment in Figure 2.2.

Dosimetric Comparisons to Conventional Radiation Therapy (RT)

There have been multiple dosimetry studies that have compared IMRT plans with those designed

**FIGURE 2.6**

Typical volumes contoured for a head and neck IMRT treatment. (A) Axial (B) 3D Rendering. This image shows some of the structures that need to be contoured prior to initiating an IMRT treatment plan. All structures must be delineated on each axial slice that it is present on. This includes targets, such as GTV and CTV, as well as normal "avoidance structures" such as the larynx and parotid glands. This is shown for both the axial slices where these are actually drawn (A) and in a 3D rendering of all of these structures (B). Structures are as described in Figure 2.3. Note the delineated normal tissue structures of parotid glands, submandibular gland, and oral cavity (purple), pharyngeal constrictors (light blue), spinal cord (brown), and margin around spinal cord ("expanded cord"; orange). The targets include base of tongue primary and gross nodal disease (pink), high risk primary CTV and high risk nodal CTV (both dark blue, as they receive the same dose), and low risk right retropharyngeal nodes and contralateral level 2 nodes (green).

using conventional methods, and essentially each investigation has shown superior tumor coverage and normal tissue sparing with IMRT. Due to its proximity to critical normal tissue structures, nasopharyngeal cancer was the first disease site to be examined for potential benefit with IMRT. For example, Chau et al performed a dosimetric comparison between 2D- and IMRT-based planning for 10 patients with advanced nasopharyngeal carcinoma and found significantly lower doses to the temporal lobe, brainstem, optic chiasm, and spinal cord; in fact, the calculated normal

tissue complication probability (NTCP) of temporal lobe damage was reduced from 11.7% to 3.4% (75). Similar results were published by investigators at University of California, San Francisco, who compared conventional with IMRT plans for 25 nasopharyngeal cancer patients, also finding significant reductions in dose to spinal cord, brainstem, and parotid gland (76).

Other disease sites may also gain a theoretical benefit from IMRT. Penagaricano et al showed improved dose conformity and less normal tissue dose with IMRT in a planning study of 3 T2

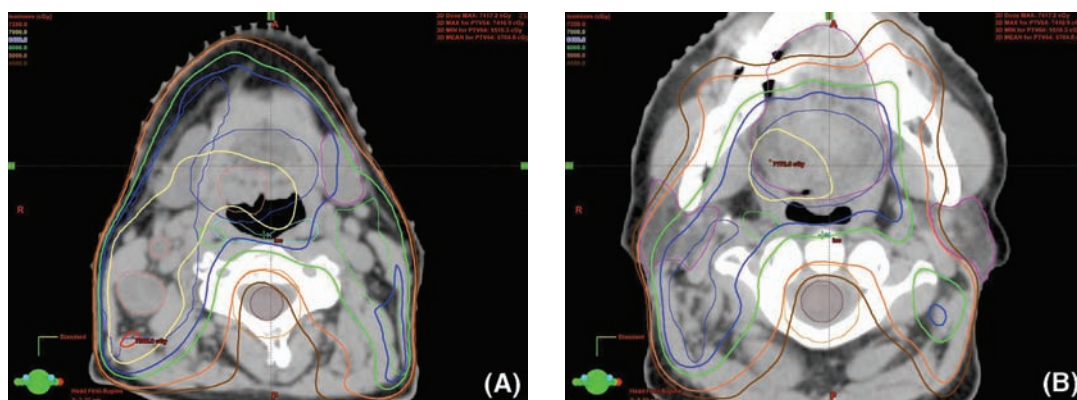


FIGURE 2.7

Axial dose distribution for an IMRT treatment. A and B represent 2 different axial levels. This shows the dose distribution for a typical IMRT treatment. Each “isodose line” represents a different dose level. Note the higher dose surrounding the target structures and the decreased doses around the dose limiting normal tissue structures. This type of dose distribution can be achieved using a combination of multiple angles (Figure 2.3) and dose modulation (Figure 2.4). Note the parotid sparing in B. Isodose lines: yellow 70 Gy, blue 64 Gy, green 60 Gy, orange 45 Gy, brown 45 Gy, and red 73.5 Gy (105% of prescribed dose).

laryngeal cancer patients (77). Swedish investigators performed a planning study in 5 hypopharyngeal cancer patients, finding a theoretical increase in tumor control probability (TCP) of 17% while significantly reducing the likelihood of late parotid injury (78). Similar results were reported by Clark et al for advanced laryngeal cancer, suggesting that multiple sites within the head and neck region could benefit from the technology (79).

These benefits do not come without a cost, as IMRT has 2 potential dosimetric disadvantages in comparison with conventional radiotherapy. First, IMRT plans generally have higher “hot spots” within the target coverage and more heterogeneity within the plan, which may lead to increased acute or late toxicity (80). These regions of higher dose arise because as the dose is pushed away from critical structures, it needs to “go somewhere,” and often it is placed within the target or non-contoured normal tissues. In a provocative article, Rosenthal et al described several acute side effects of IMRT for oropharyngeal cancer not previously

seen with conventional treatment, such as nausea and vomiting, scalp alopecia, and anterior mouth mucositis. When this group evaluated the dose to typically noncontoured, nontargeted structures, they found that IMRT delivered a significantly higher dose of radiation to the brainstem, cochlea, anterior oral cavity, mandible, and maxilla, since these organs are typically not contoured for oropharynx cancers (81). This study does highlight the unforeseen consequences of IMRT specifically, and of changing treatment paradigms without careful prospective study.

Another potential dosimetric concern with IMRT is increased dose to the larynx. In a standard 3-field head and neck plan, the central larynx can often be blocked over the course of treatment, as the junction of the opposed laterals and LAN was placed above the arytenoids. With IMRT, however, larynx dose can be significantly greater when treating a nonlaryngeal primary, even when the larynx is designed as an avoidance structure (82). Amdur et al showed that IMRT plans typically lead to more low-dose irradiation of the larynx,

and even a doubling of the mean dose to the larynx. Techniques have been developed to treat the low neck with an LAN matched to an upper field IMRT plan, thus gaining the benefit of a larynx block with parotid-sparing IMRT, but there are logistical barriers to easily enacting this in common practice (83). The long-term consequences of these worsening metrics are unclear, but it does emphasize that using IMRT does require certain tradeoffs.

The second hypothetical disadvantage with IMRT is the possibility of a higher rate of second cancer induction. Hall has postulated that IMRT may be associated with a higher second malignancy rate because it requires more monitor units (i.e., linear accelerator is on for a longer period of time) and uses more fields, thus increasing the volume of normal tissue receiving low dose (84). In fact, he has estimated that the rate of second malignancies at 10 years will increase from 1% to 1.75% with the use of IMRT (85). Radiobiologists have attempted to model this increased risk and have arrived at different results. Verellen and Vanhavere calculated that IMRT would increase the risk of second malignancies in the head and neck by a factor of 8, whereas another group suggested no difference at all (86,87). Thus, although the possibility of increased carcinogenesis should be considered, especially in younger patients, empirical data are required before accepting it as a known risk of IMRT.

Retrospective Series Using IMRT

There have been multiple retrospective series from different institutions suggesting comparable local control rates and an improved toxicity profile with IMRT versus historical controls. For example, Rades et al retrospectively compared tumor control and toxicity rates in patients treated with IMRT ($n = 18$), 3D-CRT ($n = 26$) or conventional RT ($n = 104$) (88). There was no difference in local failure, distant metastasis rate, or overall survival (OS), but the rate of grade 2 to 3 xerostomia was significantly lower after IMRT (17%) than 3D-CRT (73%) or conventional treatment (63%).

Similarly, investigators from the University of Michigan prospectively evaluated several quality-of-life metrics in head and neck cancer patients and compared the results in 10 patients who received conventional RT with 20 patients who underwent IMRT (55). Although the quality of life in both groups decreased in the first 6 months, the IMRT cohort experienced significant or borderline significant improvements in several domains, such as eating, pain, emotion, and communication, whereas there was no improvement in the conventionally treated group. By 1 year, the median xerostomia and quality-of-life scores were higher in the patients treated with IMRT, although the results were not statistically significant due to small sample size.

A larger study was reported by Graff et al, who performed a matched-pair analysis of 67 pairs of patients treated with IMRT or conventional RT and free of disease at 1 year (89). Significantly better raw scores were seen in the IMRT patients in the following areas: pain, swallowing, social eating, teeth, mouth opening, dry mouth, and sticky saliva. When these results were dichotomized into “not severe,” or “severe,” IMRT-treated patients had dramatically improved outcomes. The adjusted odds ratios (all significant) for developing the toxicity with conventional versus IMRT treatment were 3.17 for dry mouth, 3.16 for sticky saliva, 3.58 for mouth pain, 3.35 for jaw pain, 2.60 for trismus, 2.76 for dysphagia, and 2.68 for trouble with eating. Since all of these patients had no evidence of disease, a comparison of local control was not performed.

Data from Memorial Sloan Kettering Cancer Center support these findings, as their oncologic control and late toxicity results with IMRT ($n = 41$) or conventional concomitant boost RT ($n = 71$) were compared. The cancer outcomes were not significantly different, but there were significantly fewer IMRT patients dependent on gastrostomy tube (21% vs. 4%) at 2 years, and significantly fewer patients with late grade 2 or higher xerostomia (67% vs. 12%) (90).

A major concern with the dose distribution achieved with IMRT is an increased risk of

TABLE 2.1
Selected retrospective series of patients with oropharynx and nasopharynx carcinoma treated with IMRT

Institution	N	Stage III/IV (%)	Median Follow-up (Months)	Locoregional Control (%)	Overall Survival (%)	Grade 2/3 Xerostomisa
OROPHARYNX						
Mallinckrodt	74	93	33	87	87	12%/0%
MD Anderson Cancer Center	51	53	45	88	94	NR
Memorial Sloan Kettering Cancer Center	50	92	18	88	98	33%/0%
Stanford	107	96	29	92	81	NR
University of California, San Francisco	71	100	33	90	83	34%/0%
NASOPHARYNX						
China	323	80	30	94	90	8%/0%
Hong Kong	63	57	29	92	90	23% (combined 2/3)
Hong Kong	33	0	24	92	100	29% "severe"
UCSF	67	70	31	98	88	2%/0%

marginal misses due to overly conformal plans. In fact, local control and toxicity appears to be excellent with IMRT treatment for oropharyngeal and nasopharyngeal carcinoma, as displayed in Table 2.1 (91–98). As important as the absolute locoregional control rates is the fact that the vast majority of the locoregional recurrences were infield; that is, the tumor received the prescribed dose, but was resistant to it, which would have occurred with conventional fields as well. Despite these promising series, there have been sporadic reports of marginal misses with IMRT that were clearly due to PTV under coverage near a spared parotid gland (99,100). These case studies are relatively rare but need to be heeded in examining dose distributions near a spared organ.

Prospective Trials With IMRT

Two prospective, multi-institutional trials evaluating IMRT have been performed in patients with nasopharyngeal and oropharyngeal cancer. RTOG 0225 enrolled 68 patients with nonmetastatic nasopharyngeal carcinoma and treated them with IMRT-based radiotherapy or chemoradiotherapy (101). Impressively, only 7 patients experienced a locoregional failure, leading to a 2-year locoregional progression-free survival of 89.3%, and a 2-year OS rate of 80.2%. However, it is important to note that the authors attributed some of the regional recurrences to inappropriate contouring of level 5 lymph nodes, highlighting the risks of conformal therapy. Twenty percent of patients experienced a late grade 3 toxicity, but only 3% of patients experienced

grade 3 xerostomia, and only 2 patients developed grade 2 xerostomia. These results suggest that salivary preservation is possible with IMRT, without a compromise in local control.

Eisbruch et al also recently published the results of RTOG 0022, a multi-institutional trial of IMRT-based radiotherapy for early-stage oropharynx carcinoma (102). Of the 69 patients accrued, only 7 (9%) developed a locoregional failure, and 2 of those patients had underdose deviations in their plans. OS at 2 years was 96%. At 2 years following radiotherapy, there were no cases of grade 3 xerostomia, and 31% of patients had grade 2 xerostomia, again showing the efficacy of IMRT at preserving the contralateral parotid gland.

The gold standard for proving that a new treatment is superior to the prior standard of care is the randomized, phase III, clinical trial. In most centers in the United States, IMRT was quickly adopted as the technique of choice for treating head and neck cancer, and thus it has been difficult to conceive of and execute a randomized trial comparing conventional radiotherapy with IMRT. However, one trial investigating this question has been reported, and several other trials are underway.

Kam et al from the Chinese University of Hong Kong conducted a prospective randomized trial comparing parotid-sparing IMRT with 2D radiotherapy in 60 patients with nasopharyngeal carcinoma (103). Patients treated with IMRT had significantly less physician-graded xerostomia at 6 weeks and 1 year, and they had significantly higher fractional stimulated parotid flow rates and salivary flow rates throughout the study. Surprisingly, there was no significant difference in patient reported xerostomia at any of the time points (through 1 year), suggesting that the subjective sensation of xerostomia is much more complicated than a simple function of salivary output.

A second randomized trial has been performed in Europe to further investigate the benefit of IMRT in sparing parotid function. The parotid sparing intensity-modulated radiotherapy (PARSPORT) trial was performed in the United

Kingdom and enrolled patients with oropharyngeal or hypopharyngeal cancer whose tumor put them at risk for xerostomia (104). The primary end point was grade 2 or higher xerostomia, and the trial finished accruing in January 2008. Preliminary results in abstract form suggest a substantial and impressive reduction in 12 and 18 month LENT-SOMA xerostomia (74% RT vs. 40% IMRT; 71% vs. 29%) and RTOG grade 2 or higher xerostomia (64% vs. 41%; 81% vs. 20%); final results are forthcoming (105).

Techniques for Delivering IMRT

Although there are many dosimetric planning systems in commercial use, there are essentially 4 different types of IMRT delivery: step-and-shoot, sliding window, volumetric modulated arc therapy (VMAT), and helical tomotherapy.

Step-and-shoot IMRT is the simplest concept to understand, as each field (typically 7–9 per patient) at a given gantry and couch angle is simply composed of several different subfields, each with a different MLC arrangement. The leaves do not move when the beam is on (4). The sliding window method differs in that the leaves move *while* the beam is on. Although the sliding window technique theoretically increases the conformity of the treatment, quality assurance can be more difficult (106). However, data suggest the 2 methods of the treatment are comparable in terms of tumor coverage and ability to have dose verification (107).

The other 2 approaches to intensity modulation are arc-based therapies, in that the beam circles around the patient, and the MLCs change position across each arc or rotation, thus allowing sharp dose distributions. In general, VMAT is composed of 1–2 360° arcs around the patient, although they may rotate through hemi-arcs. The MLCs move throughout the arcs. Preliminary data suggest that for radiotherapy of the head and neck, VMAT is able to deliver plans with improved tumor coverage, reduced dose to avoidance structures, and use fewer than

50% the number of monitor units than sliding window IMRT (108). Conventional IMRT takes 8 to 12 minutes to complete, in comparison with VMAT, which may only require 2 to 3 minutes of beam-on time (108). However, as experience is immature with the planning software, additional study is warranted before rapidly adopting the technique.

Helical tomotherapy, of which TomoTherapy is the most widely implemented, is also arc-based therapy, although there are some features that distinguish it from standard VMAT. A TomoTherapy unit looks (and acts) like a CT scanner fused with a linear accelerator. The radiation source is a 6 MV linear accelerator that rotates around the patient in helical arcs as the patient moves through the machine on the couch. Unlike VMAT, the maximum field size for any arc is limited to 5 cm (vs. 20 cm), and the patient moves longitudinally as the beam is on. The beam is turned on at 51 different angles through any given rotation, and the treatment is composed of several rotations. The MLCs move during the arc, but as opposed to VMAT, the leaf is either “on” or “off,” such that the beam is either blocked completely by the leaf, or it is not blocked at all by the whole leaf. Another important component of TomoTherapy™ (though not a necessary part of the generic helical tomotherapy concept) is megavoltage CT imaging to set the patient up every day. Since the linear accelerator is able to perform helical rotations around the patient, the system is able to recreate a CT image of the patient and register it to the simulation CT. In principle, this improved setup process increases accuracy and could reduce the necessary PTV expansion, thus sparing more normal tissue (109). Preliminary data suggest that helical tomotherapy-designed plans are associated with improved target homogeneity and significantly reduced dose to the organs at risk in comparison with standard IMRT, including up to an 80% reduction in the theoretical late complication risk of the parotid glands (110). Preliminary comparisons of VMAT and helical tomotherapy have shown the dosimetric plans are comparable (111,112).

Image-Guided Radiotherapy (IGRT)

With the advent of IMRT and the tight margins on high-dose regions of the radiation plan (often 5 mm or less), verifying that the patient is in the correct treatment position before each fraction has become significantly more important. For example, Astreinidou et al compared PTV coverage when the hypothetical daily translational setup error was sampled from a normal distribution with a standard deviation of 4 mm, finding that the neck CTV needed at least a 5 mm margin to ensure adequate coverage (113). Similarly, investigators from University of Wisconsin recorded setup errors from 10 head and neck patients and applied those errors to the IMRT plans, showing that the error in the delivered effective dose ranged from 3% to 21% from predicted (114).

These data demonstrate the importance of minimizing setup errors as much as possible. Fortunately, patient positioning in the head and neck region benefits from excellent immobilization. In the 1980s and 90s, thermoplastic masks, which melt with heat and then harden on the patient, became more commonly used, and early data suggested superiority to older systems (115,116). More recently, masks that immobilize the entire head and neck, from the vertex down to the shoulders, have shown superiority over masks that immobilize the head alone (117).

However, masks alone do not provide adequate setup reproducibility, as one study showed that 14% of patients needed to be repositioned in a head-to-shoulder mask before treatment (118). Imaging verification of patient position is therefore crucial, and this new focus on highly precise patient setup has prompted a new term, image-guided radiotherapy (IGRT), which has been strictly defined as the use of images to monitor or modify treatment delivery (119).

In the conventional radiotherapy era, patients were positioned each day by using marks on the skin or immobilization device, delineated by permanent tattoos or marks on the mask (120). With the advent of linear accelerators, it became possible to obtain

megavoltage radiographs in the treatment position, using the treatment machine as the radiation source (120). However, the contrast of the radiograph was poor because megavoltage photons do not interact with matter via the photoelectric effect. More recently, kilovoltage imaging systems have been attached to linear accelerators, providing significantly enhanced contrast in the portal images (120). Pisani et al performed both MV and kV port films before each fraction and found that kV imaging significantly reduced setup error in head and neck patients (121). Nevertheless, although kilovoltage imaging provides slight improvements over MV films, patient setup errors with standard megavoltage port films are quite small, typically less than 4 mm, in part because head and neck patients are rigidly immobilized (114,121).

The most recent innovation in patient positioning is volumetric imaging, which images the tumor and surrounding organs at the time of radiation delivery (120). One of the first tomographic approaches to volumetric imaging was an integrated linear accelerator—CT scanner (“CT on rails”), in which CT was performed in the treatment position and then used for patient positioning (122). However, these systems are bulky and require the couch to move or rotate to allow the CT to obtain the images. A more commonly implemented technology is cone beam CT (CBCT), in which 2D radiographs produced by an MV beam (i.e., the linear accelerator) or attached kV imager are reprocessed to create a rough CT image (120). These images are far from diagnostic quality but are sufficient for superb patient positioning. For example, Den et al showed that CBCT could reduce the PTV margin used in head and neck cancer by roughly 2 mm to 3 mm in comparison with setup from orthogonal radiographs (123).

It is important to recognize that even with cone beam CT imaging, setup error will never be zero. Preliminary studies with cone beam CT have found that despite rigid immobilization in a thermoplastic mask, several volumes in the head and neck have many degrees of freedom that are not detected on plain imaging. For example, van

Kranen et al performed regular CBCT on 38 head and neck patients and assessed setup error in several regions of interest, such as the mandible, larynx, occiput, jugular notch, and several levels of cervical spine (124). Although the mean setup error and its standard deviation were 1.2 mm and 1.5 mm, respectively, while using the entire image for registration, the errors of the specific substructures varied substantially, from 1.1 mm (C1-3) to 3.4 mm (larynx). Similarly, Polat et al performed CBCT before 100 fractions in 11 patients with head and neck cancer (125). After isocenter alignment using the whole CBCT, the skull and mandible were found to have moved a mean 4.7 mm and 4.4 mm, respectively, in comparison with the planning CT. These findings highlight the deformation that occurs in the head and neck due to subtle changes in neck and chin position.

Another key component of IGRT is adaptive radiotherapy, which is the modification of the radiotherapy treatment plan based on a change in patient contours (either tumor volumes or normal tissue structures) (120). Investigators at MD Anderson Cancer Center performed serial CT scans over the course of radiotherapy treatment for 14 patients with head and neck cancer, finding that the GTV decreased by 69.5% at the end of treatment, and the parotid glands decreased in volume (28.1% smaller by the end of treatment) and shifted medially (126). These results suggest highly conformal IMRT plans could result in final GTV and parotid doses significantly different from initially planned. In fact, this same group then performed a similar study in patients receiving IMRT and showed that over the course of therapy, the mean dose to the parotid increased by 5 Gy to 7 Gy in 45% of patients, again highlighting the potential role of adaptive radiotherapy (127).

The potential dosimetric errors associated with significant changes in patient contours was also shown by Hansen et al, who analyzed the plans of 11 head and neck patients who required replanning of their head and neck IMRT plans due to significant weight loss or tumor shrinkage (128). This group found that without replanning, the doses to

95% of the PTVs were reduced in 92% of patients (up to 7.4 Gy in one patient), and the dose to the spinal cord increased in all patients, and the dose to the brainstem increased in 85% of patients. These findings were echoed by a prospective study by Kuo et al, who replanned 10 head and neck patients after 45 Gy. The mean dose to the parotids was reduced, on average, by approximately 3 Gy, a benefit that may reduce long-term xerostomia risk (129).

The potential to tailor the IMRT plan to each patient's response and weight loss is tantalizing, but much work remains to be done on the approach. It is critical to determine which patients will benefit the most from replanning, and more importantly, whether shrinking the high-dose region to accommodate tumor shrinkage compromises local control.

Particle Therapy

With the proliferation of proton beam therapy centers across the country, there has been much interest in taking advantage of their dosimetric properties for head and neck cancer. However, there are actually significantly more prospective data published on the use of neutron beams for treatment of head and neck cancer.

The theoretical benefit of neutron beam therapy lies in its high linear energy transfer (LET), meaning it deposits 20 to 100 times more energy along its path than photon, electron, or proton beams. The dose distribution of neutrons is comparable to that of photons, with a relatively slow fall off from its depth of maximum dose (130). Increasing dose to the tumor should intuitively improve local control, but unfortunately normal tissue also responds more robustly, thus limiting its therapeutic ratio. Several randomized trials investigating the role of neutron therapy in squamous cell cancer of the head and neck have been published (131–133). There was no significant oncologic benefit to neutrons, but the rate of severe toxicity was significantly greater in the neutron

arms (40% vs. 17% in one trial), effectively ending the investigation of neutron therapy in this disease (131).

In contrast, the results with neutron therapy have been more favorable for salivary gland malignancies, which are known to be more radioresistant. Single institution retrospective studies have suggested over a doubling of the local control rate with neutron therapy, prompting a randomized controlled trial (130). The Radiation Therapy Oncology Group-Medical Research Council (RTOG-MRC) randomized controlled trial of neutron versus photon therapy for inoperable salivary gland tumors was stopped after only 32 patients were entered, as the local control rate was 56% for neutron therapy and only 17% for photon therapy. However, there was no difference in OS due to the development of metastatic disease, and this futility, in addition to the scarcity of neutron therapy centers, has led to little enthusiasm for neutron therapy in this disease (134).

Proton beam radiotherapy, on the other hand, has significant dosimetric advantages over photon and neutron beams, thus holding the promise of exceptionally conformal radiotherapy (135). Proton penetration into tissue is defined by the Bragg peak, where the vast majority of its dose is deposited in a very small volume, and the tissue in front of and behind the Bragg peak receives very little dose. By modulating the energy of the protons and “spreading out” the Bragg peak so that more volume is irradiated, a highly conformal dose distribution can be achieved. For all intents and purposes, the biological efficacy of the proton beam is nearly identical to that of photons. However, since the dose is so much more conformal to the target volume in comparison with photon treatments, the same dose can be delivered to the tumor while depositing less dose to normal structures, or a higher dose can be delivered to the tumor while depositing the same dose to the normal structures. In either scenario, the therapeutic ratio is theoretically improved with proton therapy.

Currently, proton therapy is almost always delivered using a “passive scattering” technique, in

which each proton beam passes through a lucite compensator to achieve its required dose distribution. Each plan is composed of several of these beams, each with its own compensator. However, the next generation of proton therapy will treat patients using a “pencil beam,” or “scanning beam,” technique, in which a very small circular beam of protons is scanned throughout the treatment field; each beam has its own energy and intensity, such that each voxel in the target volume can receive a different dose (136). One principal benefit of the scanned beam is the ability to perform intensity-modulated proton therapy (IMPT), which is the proton equivalent of IMRT (136).

To our knowledge, there have been no comparisons of passive beam proton dosimetry with IMRT, but the dosimetric benefits of IMPT have been evaluated in several studies. Thorwarth et al performed comparisons of IMPT and IMRT in 3 head and neck cancer patients and showed that IMPT produced more conformal tumor coverage and significantly less irradiation of normal tissue than photon-based IMRT (137). Steneker et al confirmed these results, finding significantly lower parotid doses and integral doses with IMPT in comparison with IMRT plans with the same homogeneity (138).

Although the dosimetry of proton beam therapy appears superior in comparison with IMRT, several caveats must be minded. At the most basic level, the more conformal a radiation plan, the higher the risk of geographic miss, and proton therapy is clearly the most conformal treatment available. The radiation oncologist must therefore be extremely confident with his or her contours as there is such a steep dose falloff beyond the target volume. In addition, proton therapy tends to deliver increased dose to the skin because there is no skin-sparing buildup in particle therapy (139). Although this problem is lessened with scanned protons, the significant dermatitis incurred by chemoradiotherapy makes it critical to assess whether proton therapy is even feasible for tumors in the head and neck.

The uncertainties in proton dosimetry also need to be considered. First, proton paths through

air cavities are particularly challenging to model, and head and neck cancers have significantly more air cavities than intracranial targets (140,141). Second, despite rapidly developing computer software, there is still some uncertainty in the location of the Bragg peak (141,142). Thus, even if the volumes are perfectly contoured, highly conformal proton radiotherapy does run the risk of geographic miss due to dosimetric inaccuracies. Finally, there is the biological uncertainty in the relative biological effectiveness (RBE) of protons at the Bragg peak (143). If the RBE of the proton beam is higher at the edge of the beam, there is the possibility of increased late tissue damage, similar to neutrons; only empirical data can show whether this hypothetical concern has merit.

There are limited clinical data on the use of proton radiotherapy in head and neck cancer. Only one prospective trial has been published. Investigators at Loma Linda University performed a phase I/II trial evaluating the use of a proton boost in an accelerated radiotherapy regimen for patients with oropharyngeal cancer; the primary disease was boosted to a total of 75.9 cGy (Cobalt Gray equivalents). The actuarial 5-year local control rate was an impressive 84%, and crude late grade 3 toxicity was 11%. These results are particularly impressive given that more than half of the tumors were T3 or T4, and no chemotherapy was given (144). Unfortunately, no other prospective trials have been reported thus far.

■ SUMMARY

Radiotherapy delivery has undergone a technological revolution over the past 20 years, primarily driven by intensity-modulated radiotherapy. Data are accruing that these innovations may lead to comparable tumor control with a reduction of long-term toxicities, thus improving the therapeutic ratio. The next generation of technical advances in head and neck radiotherapy will probably involve particle therapy and adaptive radiotherapy, which aim to further reduce normal tissue dose while delivering tumoricidal doses to gross and subclinical

disease. However, the cost of progressively higher conformality is the risk of local recurrence (LR), and prospective trials are necessary to establish the safety of these new techniques.

■ FRACTIONATION

“Fractionation” refers to how a course of radiation therapy is delivered over time. It is described by (1) the dose delivered per treatment or fraction, (2) the total dose delivered (equal to dose per fraction times total number of fractions), and (3) the total duration, in days, of the course of therapy. The clinical factors addressed by altered fractionation, control of rapidly proliferating tumors and minimization of late effects of radiotherapy (145) are critical issues in management of SCCHN, and fractionation has been studied extensively in this setting. Integrating the current techniques and technology of radiation therapy delivery with the data acquired and lessons learned from prior fractionation studies raises important questions and challenges. IMRT and its current usage have led to very different models for how to prescribe and deliver dose than those employed in the fractionation studies, almost all of which used the classical 3-field head and neck radiation technique. In addition, in the modern era, precise delivery methods and systems allow us to alter our radiation schedules if treating limited tissue volumes. One can also consider hypofractionated treatment in certain clinical situations, using a small number of large, highly conformal fractions. This type of treatment had previously only been available for radiation treatment of the central nervous system.

Evolution of Fractionation/Integration With Current Radiation Methods

Standard fractionated radiation for SCCHN is considered to be once daily treatment over 7 weeks for a total dose of 70 Gy using 2.0 Gy daily fractions. There are 2 primary reasons for using altered fractionation radiation therapy. First, accelerated

fractionation can address tumor kinetics—this approach delivers the same radiation dose in a shorter total time, in order to account for the fact that tumor cells are growing during treatment. An example of this approach is the accelerated fractionation/concomitant boost regimen, which delivers 72 Gy in 6 weeks using a combination of 1.8 Gy and 1.5 Gy fractions, as pioneered at MD Anderson. Second, hyperfractionation theoretically minimizes late complications while increasing the total dose—it employs smaller doses per fraction given more than once per day. Larger fraction size is a strong predictor of late complications for a given dose of radiation. The goal is to keep the chance of a late complication constant, but it allows the total dose to be increased, thus increasing the chance of tumor cure. An example would be a 120 cGy BID regimen to a total dose of 81.6 Gy, which is commonly used at the University of Florida.

For treatment of SCCHN, the data supporting the benefit of altered fractionation radiation is compelling, coming from phase II, as well as a phase III study and from meta-analyses (146–151). Perhaps the strongest evidence comes from the definitive results of RTOG 90-03, a multicenter Phase III trial, which enrolled more than 1,000 patients in a 4-arm study of 3 different fractionation schedules and a standard-fractionated control. All patients were treated with non-IMRT external beam radiation. The results of this study indicated a local control benefit for both of the regimens described above when compared with standard fractionated radiation. As expected, both schedules were associated with an increase in acute toxicity. It is universally accepted that for patients with locally advanced SCCHN treated with radiation alone, altered fractionation needs to be used. However, virtually all the studies focusing on determining optimal fractionation schedules have been performed without systemic therapy. It is important to note that this is true of virtually all the fractionation studies, not just RTOG 90-03. In addition, the radiation treatment in all these trials has been delivered using standard 3-field and conformal techniques, that is, not with IMRT.

Each of the different treatment paradigms for radiation-based therapy—altered fractionation, IMRT, and addition of systemic therapy—seeks to identify a version of “optimal” therapy based on the tenets of that particular treatment model. Studies of concurrent systemic therapy, which are addressed in more detail in other chapters of this book, have demonstrated that addition of systemic agents, either traditional chemotherapeutic drugs [e.g., (152)] or “targeted” agents [e.g., (153)], consistently improve local control and in many circumstances also show a survival advantage. However, none of the studies to date that have looked at concurrent systemic therapy have used IMRT. Similarly, the studies of highly conformal radiation delivery techniques, such as IMRT, have looked at toxicity and local control in the context of differential dosing or “dose-painting” treatments rather than the conventional shrinking-field radiotherapy. With this modern approach, each of the different targets receives a different dose, making it difficult to determine what fractionation data is most appropriate. We will now address how varying these parameters can be taken into account for integration with fractionation in the modern era of SCCHN radiation.

Integration of Fractionated Radiation With Systemic Therapy

For definitive treatment of locally advanced SCCHN, it is well established that optimal therapy based on standard fractionated radiotherapy requires the addition of concurrent systemic therapy (154). The choice of appropriate concurrent agents is drawn from 2 areas: drugs shown to have intrinsic efficacy in treating SCCHN and drugs that have demonstrated radiosensitizing properties. There is frequently an overlap between the 2 groups of agents. Data supporting the efficacy of concurrent therapy are available in a range of studies using a wide variety of agents. The most commonly used concurrent agent is cisplatin, typically given as a bolus of 100 mg/m² every 3 weeks, though weekly use is also being investigated.

Since both altered fractionated radiotherapy and concurrent systemic therapy show improved oncologic outcomes, the next logical step would be to combine them. The most appropriate way to achieve this synergy is unclear, and that such an aggressive combination would even succeed is a bigger question. The model most frequently used to investigate adding systemic therapy to standard fractionated RT is to compare outcomes for a patient population with or without drug given concurrently with standard fractionated radiation. An example is Starr et al (155), who looked at a concomitant boost type schedule of 1.8/1.5 Gy fractions to total doses of 69.9 Gy to 72 Gy for locally advanced SCCHN in oropharynx and hypopharynx patients. There was clear evidence of a benefit for oropharynx patients, as compared with hypopharynx patients, where there did not appear to be much benefit to the combined trial program. The underlying reason for this is not apparent, but certainly does point out that the biology of these distinct anatomic sites may be quite different. As expected, significant toxicity was seen with both arms, greater in the combined arm. The authors do not make a clear conclusion about the benefit of using both systemic therapy and altered fractionation together.

Another approach is to match the toxicity levels in the 2 arms of a study. In this scenario, a lower radiation dose would be used when adding systemic therapy. Most commonly, standard radiation treatment schedules, such as hyperfractionation or concomitant boost as described above are used as the basis for a combined modality study, though some groups will investigate variations of standard fractionation schedules. An example is Brizel et al (156), who looked at a fractionation schedule of 1.25 Gy given BID with or without systemic therapy. The radiation-alone arm used a total dose of 75 Gy, whereas the arm using concurrent cisplatin and 5-FU had a total radiation dose of 70 Gy. This study demonstrated a local-regional control and survival benefit for the combined arm.

These studies both ask the question of what and how much does systemic therapy add to the

established benefits for altered fractionation. They are representative of a number of such studies. Another way to approach this important question is as follows: We start with the information that systemic therapy improves outcomes when added to radiation. Then, the question we ask is: Is there a marginal benefit from adding altered fractionation? In RTOG-0129, all patients received bolus cisplatin and were randomized in 2 groups: (1) Arm A patients received SF of 2.0 Gy to 70.0 Gy over 7 weeks, and (2) Arm B patients received the standard concomitant boost regimen of 1.8/1.5 Gy to 72 Gy over 6 weeks. Even the simple design of this study indicates how difficult it is to balance all variables in a combination altered fractionation/systemic therapy trial. Cisplatin is given as a bolus every 3 weeks; thus, 1 group will receive 2 cycles of chemotherapy and the other the standard 3 cycles. The results of this trial have been released in abstract form (157), indicating essentially equivalent locoregional control and survival for the 2 arms, suggesting that there is no marginal benefit to adding altered fractionation to CRT.

Integration of Fractionated Radiation Therapy With IMRT

External beam radiation for SCCHN is clearly moving in the direction of contour-based, inverse-planned approaches, such as IMRT, as standard therapy. In this setting, the best way to make use of the many years of fractionation data remains a challenge. On the simplest level, we could follow the classic “shrinking field” cone down model for treatment using IMRT instead of standard fields. The IMRT fields could be used to deliver a well-sculpted homogenous dose to all structures at once, and a series of cone downs, or shrinking fields, used to obtain the dose differential that we desire between the 70 Gy to gross disease and the lower doses used for the at risk volumes. With this approach, we can just transfer all of the fractionation information, such as expected control rates

and toxicities from 2.0 Gy/day to 70 Gy and how to use 1.8/1.5 Gy fractions in combination with doses of 72 Gy. Although comforting, this approach has some clear limitations and is contrary to standard practice, which uses dose painting. One issue is the time involved in planning, setting up, and performing quality assurance for each individual IMRT plan. If this model is used, a standard head and neck treatment could require as many as 3 IMRT plans. This approach has seen limited use in some centers and in certain protocols allowing both IMRT and standard techniques. However, it would potentially overburden staffs and thus be an unreasonable approach to use as standard therapy. In addition, as the treatment planning systems are currently configured, this may not yield optimal treatment plans, as the algorithms for the inverse planning associated with delivering IMRT are designed to achieve optimal plans for each course. These systems typically cannot optimize all 3 plans simultaneously. Plan optimization can accommodate dose delivered previously, but this approach raises questions as to whether an optimal overall result is obtained.

If the classic field reduction technique is not used, and it typically is not if IMRT is employed, the single IMRT plan with differential dose delivery or “dose painting” will be chosen to deliver treatment. However, the basic question remains: In order to achieve the known cure and toxicity rates, what total dose should be used, delivered at what fraction size to which different targets? As these targets, as well as the normal tissue structures, will be receiving different daily doses, from which database should this information be drawn? Another consideration relates to the biology of the smaller fractions delivered when “dose painting” is used with 1.5 Gy or 1.2 Gy daily fractions. If the daily prescribed dose is 2.0 Gy, secondary targets will typically receive from 1.6 Gy to 1.8 Gy per day. However, if the individual fraction size is 1.2 Gy, lower dose targets are receiving less than 1.0 Gy per fractions, and we do not have any data to allow us to determine the efficacy of such small fractional doses.

The simultaneous integrated boost (SIB) approach attempts to incorporate the information from fractionation studies into the standard model of differential doses for IMRT delivery (158–160). Using SIB still delivers treatment on a once daily basis but delivers larger fractions (>2.0 Gy per fraction/day) to gross disease. This accelerated radiation dose addresses tumor repopulation, delivering a given dose in a shorter period of time. However, the individual fraction size is bigger; at least in theory minimizing the benefit in late toxicity seen when giving more than 2.0 Gy/day split between 2 daily fractions. Basic radiation biology tells us that toxicity is a function of the size of each individual fraction. Therefore, to some degree, the use of SIB requires discarding the years developed from the altered fractionation schedules that we know are safe and effective. One way of getting around this, which offers a compromise, is the DAHANCA (Danish Head and Neck Cancer Group) schedule. In this approach, 6 fractions of treatment are given over the course of 5 days. This study was carried out with traditional radiation delivery techniques but is quite easily translated to the IMRT delivery approach. It offers the benefit of increased dose per week and thus increased tumor control probability, but the maximum dose from an individual fraction is still 2.0 Gy. As expected, the results using this technique show increased transient acute toxicities, but have not documented change in more concerning late complications (161). Disease-free survival was improved for the 6 fraction a week schedule (70% vs. 60%; $P = .0003$) with benefit seen in terms of primary sited control, but no effect on nodal disease control.

Interaction of Improved Radiation Delivery and Altered Fractionation

If we view the impact of fractionation in the context of the new technology, from a different perspective, we have the basis for a distinct treatment algorithm that is the use of “hypofractionation.” This approach is similar to what is done in stereotactic radiosurgery (SRS) and is gaining popularity

as SBRT or surgery. Earlier technology has allowed this type of treatment to be used in head and neck, but often in very limited circumstances. For example, a head and neck lesion adjacent to the skull base could frequently be treated with standard SRS, as used for CNS lesions (162). This approach was applied as a radiation boost in upfront or recurrent nasopharynx cancers. The current technology allows the application of hypofractionation to the treatment of head and neck malignancies in a range of clinical situations. There are multiple platforms that offer the ability to deliver high dose, highly conformal treatment to limited volumes. The currently available systems will also allow for larger volumes to be treated than those used for SRS.

The clinical situations in which we would consider using this would be for radiation boosts or in the treatment of recurrent disease. For example, a range of technologies have been used for either single fraction or repeated highly conformal treatments of skull base malignancies. There are published data from the CyberKnife system using limited fraction for treating recurrent disease (163). A remaining question here, as for other disease sites, is: What is the optimal fractionation of such hypofractionated regimens?

■ MULTIDISCIPLINARY CARE AND RADIATION THERAPY

An essential component of optimal oncologic care is multidisciplinary evaluation and integrated treatment planning. Although this approach yields the best outcomes in most malignancies, this paradigm is particularly important in treating head and neck cancers. Interaction and communication with surgical and medical oncology colleagues is a critical function of radiation oncologists, given the central role the specialty plays in the modern management of SCCHN. The input of each specialty and its intrinsic expertise is necessary for an appropriate decision on initial, recurrent, or even postoperative management. For example, the choice of an initial therapy has implications for the patient’s subsequent

treatment options should a recurrence develop. Any single modality can have an impact on the delivery of complementary modalities, and it is critical to remember this interrelationship during the decision-making processes.

Multidisciplinary Consultation

The first step in delivery of appropriate care for a SCCHN patient is a multidisciplinary consultation. Specialists who always need to be involved include radiation, medical, and surgical head and neck oncologists. Ideally, dentists, speech and swallow therapists, and nutritionists are readily available, even if not present at the time a patient is first seen.

The first component is the initial physical examination by the multidisciplinary team, where each member can have “value added” to the overall process. The radiation oncologist must be appropriately trained and comfortable with carrying this out on their own, but the presence of a team will optimize the information obtained. Even with the best imaging, factors important to appropriately designing an overall course of therapy can only be determined by clinical examination. An example of this synergy is the description of initial disease extent, which greatly influences how the radiotherapy is delivered. In many cases, this information cannot be obtained from even the most detailed imaging. There are small volume/rapid transitions of normal critical structures, which can greatly influence the areas that require treatment. For example, small volume mucosal or submucosal changes—the presence of which can significantly alter treatment planning—can be detected through a careful history or physical examination but may be missed on any cross-sectional or functional imaging. For example, functional changes, such as those resulting from clinical perineural invasion, can be picked up both on detailed history and careful physical examination. These findings, often subtle, can also significantly alter volume and dose prescriptions through their effects on expected avenues of disease spread.

The importance of multiple examiners evaluating a patient is exemplified in a study from MD Anderson, where all patients are examined and IMRT contours are reviewed in a conference by all head and neck radiation oncologists before the planning process begins. A surprising number of cases initially contained errors—66% of treatment plans had minor changes, whereas 11% of the changes were major, which could potentially lead to adverse cancer or toxicity outcomes. This study clearly showed the positive impact that occurs when multiple practitioners provide input into physical examination findings and tumor contours (164). In this particular study, all the participants were radiation oncologists with expertise in treating SCCHN; most centers do not have this depth of expertise within the radiation oncology department itself. However, some of it can be derived from other experienced experts, as obtained in a multidisciplinary consultation.

In addition to specifying the details of the initial presentation, each of the specialists contributes to final decisions as to the best treatment plan for a patient. An individual’s overall health and performance status, as well as specific physiologic or anatomic features can significantly influence the decision making. For example, renal dysfunction may render a patient a noncandidate for cisplatin, possibly leading to the use of a different agent or a more intensive radiation-alone schedule. Assessment of swallowing function, based on anatomic distortion from the tumor, or assessment of a barium swallow, may indicate that laryngeal function has been lost to such an extent that the aspiration risks following a nonsurgical, radiation-based approach outweigh the quality-of-life benefits of avoiding laryngectomy. The information gained by the radiation oncologist and his/her input at this time is invaluable to the patient receiving appropriate treatment, particularly if a modality other than radiotherapy is to be delivered as the initial therapy. This model has historically been the tradition and practice for patients who will receive initial surgery. Some patients will not require postoperative therapy, but for those who will, a

preoperative evaluation can be invaluable to the radiation oncologists in treatment planning. In current practice, there is also a huge impact on the requirements for irradiation in a patient who receives induction chemotherapy. There are many detailed technical implications of this decision, which will be addressed below. However, there are also many important features to the decision-making process. A decision to treat a patient with upfront chemotherapy must be made by all of those treating the individual—the medical oncologist who will deliver the drugs, the radiation oncologist who will deliver the definitive therapy, and the surgeon, who may be called upon to perform a posttherapy neck surgery or subsequent biopsy of a primary site. Decision making by the first person to see the patient is to be avoided at all costs for both sociological and medical reasons. Any patient receiving induction chemotherapy must be seen by a radiation oncologist prior to initiating therapy.

Radiation Therapy and Surgery

Surgery and radiation therapy are the 2 primary modalities for local and regional management of SCCHN, and as a result there are longstanding patterns of interaction between the specialties. The final decision regarding the use of radiotherapy in postoperative management of SCCHN involves discussions between the head and neck surgeon and the radiation oncologists about the nature of the surgery as well as evaluation of a number of pathologic parameters. Adjuvant radiotherapy with concurrent bolus cisplatin is the class I-recommended standard treatment in certain well-defined high-risk postoperative scenarios (165,166), though other combinations are being actively investigated (167). In addition, surgery remains the definitive diagnostic and therapeutic intervention for radiotherapy-treated patients with residual disease in the primary site or lymph nodes.

An important issue in modern postoperative radiation delivery has been alluded to in the earlier sections: that of the volume definitions. The

decision on what volumes to irradiate was complex even in the era of 3-field radiation delivery, and target definition takes on broader significance with highly conformal radiotherapy. It involves preoperative patient evaluation, discussions with the surgeon, and review of the operative/pathological findings. The treatment volume often encompasses an extensive region, including all of the tissue manipulated by the surgical procedure, which is at risk of harboring microscopic diseases. Similar to the situation in upfront management, this task has become more complex with the requirement of a contour-based approach. Delineating volumes on individual axial slices requires much more decision making, although this does have the benefit of more clearly indicating where a procedure has been done. Universally accepted guidelines have not been established for contouring postoperatively as there has been for volume definition in definitive treatment. There has, however, been a publication making suggestions for how the post-op (and N-positive) necks are to be contoured, which can aid the slice-by-slice decision making (168).

This issue of defining appropriate volumes has been the subject of retrospective trials asking the question of whether control rates with IMRT-based adjuvant treatment are as effective as prior techniques. Most of the data indicate no decrement in outcome with IMRT. Two studies with a modest number of patients looked at this question for a range of HN tumors sites. Rades et al (169) retrospectively studied 148 post-op patients treated with IMRT, 3D, or conventional techniques, with a minority receiving systemic therapy. A range of prognostic factors were assessed, and no difference of outcome was seen across different delivery techniques. No differences in acute or late toxicity were noted, but a significant decrease in xerostomia was described for the IMRT patients. In a study of 71 patients, Studer et al (170) found excellent local-regional control rates compared with historical controls and found that all failures were in the high dose IMRT region, indicating that inadequate target definition was not the etiology of the recurrences. One study has actually looked

at a combination of IMRT, concomitant boost (6 standard fractions in a week) and bolus cisplatin combined postoperatively with good LR control (171). This study grouped together a range of primary sites. The majority of postoperative HN radiation is performed for oral cavity (OC) tumors and this is where most of the studies have focused.

The published OC studies are more focused in terms of disease site, but share the limitations of the broader studies in being retrospective. Studer et al (172) examined 58 IMRT treated OC patients, with 28 being treated postoperatively. Post-op IMRT patients fared better than historical controls treated with 3D techniques (92% vs. 80%). They also showed that postoperative OC patients did as well as postoperatively treated oropharynx patients (both >90%). Yao et al (173) reviewed the University of Iowa experience for OC tumors, with 49/55 being treated postoperatively. A total of 12 patients had a component of LR failure (9 LR alone, 3 LR with distant metastases [DM]), and except for one who failed in an untreated contralateral neck, all failed in high-dose region, with the presence of extra capsular extension (ECE) being a particularly strong poor prognostic factor. The Memorial Sloan Kettering Cancer Center data for 35 post-op OC patients (174) demonstrated 5 LR recurrences and overall acceptable acute and late toxicity. Chen et al (175) compared conventionally (27 patients) and IMRT (22 patients) treated postoperative OC patients. The OS, disease-free survival (DFS), and acute toxicity were comparable for the 2 techniques. However, the IMRT-treated patients did show an improvement in terms of late toxicity with less xerostomia and dysphagia compared with the conventional radiation. In general, these studies show LR control is maintained and there is a decrease in morbidity when using postoperative IMRT.

Radiation Therapy and Systemic Therapy

Systemic therapy has an increasing role in the management of advanced SCCHN in combination with radiation treatment. Two different temporal

combinations are used: We will focus on (1) the radiation therapy issues in concurrent chemoradiation, and (2) questions that arise regarding the use of induction chemotherapy. The emphasis will be on how radiation doses and volumes should be altered as a consequence of the use of systemic therapy.

Concurrent Chemoradiotherapy

The most frequently used combination of systemic therapy and radiation is concurrent chemoradiotherapy. A range of systemic agents are used in this model, chosen for their radiosensitizing and/or efficacy toward SCCHN. When using this approach, 2 different models are considered to determine the appropriate radiation dose. Typically, the radiation dose delivered is not changed from the doses delivered if radiation alone is used and chemotherapy is added to this (e.g., SF with 2.0 Gy to a total dose of 70 Gy $\pm$ systemic therapy). Less frequently, the radiation dose is lowered to reflect the use of the systemic therapy, which will contribute to both efficacy and toxicity of the treatment combination. Radiation therapy remains the primary curative modality in these combinations, and it is critical not to compromise its delivery with whatever combination of systemic agents is chosen.

The treatment volumes in the combined modality setting are essentially unchanged by the addition of concurrent systemic therapy. Treatment is still being delivered to an untreated and undisturbed tumor. Thus, the same anatomic volumes contain tumor and are at risk for harboring tumor cells, and these still require treatment. It is accepted that certain chemotherapy agents are associated with more toxicity with concurrent treatment, such as 5-FU or the taxanes; in theory, the use of these drugs could potentially impact the recommended doses, though this is not usually done in practice. Thus, the addition of concurrent chemotherapy changes very little about how the radiation therapy is delivered.

Induction Chemotherapy

In contrast with concurrent chemoradiotherapy, using systemic therapy prior to radiotherapy can

have a significant impact on radiation planning and treatment delivery. The induction approach is gaining favor, but its use remains controversial and is not as widely employed as combined chemoradiotherapy. This pattern of care is driven in part by the skepticism much of the radiation oncology community still has about this approach. Thus, due to its lack of broad acceptance, many of the relevant questions regarding radiation in the post-induction chemotherapy (IC) setting have not been answered. Most of these questions, in fact, have not been asked now or in the prior era of radiation. The planning issues are exacerbated in the era of IMRT. In the early studies, less attention was paid to the details of the radiation component of this multimodality treatment. Thus, we are at a point now where the use of IC is increasing, but exactly what to do with the radiation treatment volumes is uncertain.

Induction chemotherapy typically results in shrinkage of both the primary and lymph node disease. Although a decreased tumor burden is a benefit, there remains a complicated question of what volume needs to be treated and to what dose. The standard model has been to treat the initial disease distribution both in terms of dose and anatomic extent, essentially as if no treatment had been delivered. This was easier to carry out in an era when a 3-field treatment approach was used. The current contour-based radiation treatment of SCCHN requires the physician to make a determination of what should be identified as a target and what should not on each axial image. If a 5 cm hypopharynx mass has decreased to 1 cm, or is no longer visible, what is the "GTV"? Similar issues are present for the cervical lymphadenopathy. It is not a straightforward exercise to determine where the tumor masses were at the initiation of treatment and transfer that information to the current anatomy. As noted previously, just the delineation of the targets can be challenging for head and neck patients, even without the added burden of altered anatomy. The challenge of this component of IC is underappreciated by medical oncologists and not recognized by radiation oncologists until

they attempt to carry it out. Recently, consensus recommendations on how to do this have been presented in an attempt to establish some basic guidelines (176). These are helpful, but in the absence of an identifiable mass, it remains difficult to determine what gross disease was and thus what the high-risk region is. A possible technique, which might help with this process, would be a version of adaptive therapy, which could help to transform the initial contours, including GTV and high risk CTV to the final planning CT images. Regardless of the method used, volume delineation needs to be based on preinduction tumor extent. It is thus essential that radiation oncologists have imaging and perform a physical examination before any treatment has been delivered.

Beyond the difficulties of actually contouring targets in the postinduction setting, an array of questions need to be answered regarding radiation treatment given after induction chemotherapy. The only model we have is to treat as if no therapy had been given, in order to not compromise local control. However, IC is being used more frequently and the most active current regimens have demonstrated increased activity relative to the previously used standard IC regimens. As IC shows increased efficacy, it may be time to consider testing the fundamental radiation issues in a protocol setting. These questions include what is the appropriate target volume and what is the appropriate dose for a GTV that has a partial response (PR) or a complete response (CR) to IC. Another question is how to choose the factors that will determine the intensity of the radiation-based treatment delivered? There are several approaches to this question. Our Dana-Farber group tailors the intensity of the radiotherapy to the degree of response to induction. The basis for this is the early induction studies (177,178), showing outcomes as a function of how a patient responds to initial therapy. Those patients having a pathological CR did better than those who did not, independent of clinical examination. Thus we increase the intensity of locoregional therapy in patients who do not have a good response to IC by altering the concurrent

chemotherapy or accelerating the irradiation schedule. Of note, there are no data supporting a decrease of the radiation dose from the levels used in definitive therapy, regardless of how good the response is to IC. In contrast with this approach, the MD Anderson Cancer Center group determines the intensity of the radiation dose based on the initial tumor stage of the disease, independent of the extent of response.

Toxicity Considerations

Since the earliest uses of radiation as the non-surgical, organ-conserving curative treatment of SCCHN, the well-established “cost” of the treatment is short- and long-term local toxicity. A number of factors have brought this issue to the forefront when considering recent advances and current management of head and neck cancers.

The 2 improvements in radiation treatment paradigms, concurrent chemoradiation and altered fractionation, both demonstrate increased local toxicity associated with the improved locoregional control. These data come from individual trials using a range of systemic agents and varied fractionation schedules. Meta-analyses also offer strong support of this findings; this analytic technique is a powerful tool in SCCHN, as trials can be fairly modest in size and pooled data can often reveal definitive information not obtained from the individual studies.

These studies have mostly been performed with traditional 3-field radiation techniques, and thus it is not straightforward to apply the data to current techniques. In addition to the intrinsic toxicity of radiation, it is well established that there can be additional and unexpected toxicities from delivering IMRT. For example, if a dose of 70 Gy is delivered to the tumor and there is a parotid-sparing plan, additional dose will be deposited in the tissues of the head and neck, often at unexpected sites. From the earliest use of IMRT, there have been anecdotes regarding unexpected toxicities. In addition, these toxicities have been investigated in small studies. Sanguinetti

et al examined mucosal toxicity, comparing IMRT with standard planning techniques (179). They showed that additional mucosal toxicity was caused with IMRT plans unless oral mucosa was specified as an avoidance structure. In this latter case, IMRT was associated with decreased mucositis. Monroe et al identified young age and dose to the dorsal vagal complex of the medulla as a new risk factor for nausea with IMRT (180). These studies also emphasize one of the benefits of contour-based planning, in that detailed dose-response relationships can be evaluated and used to establish guidelines and tolerances, which may help to limit toxicity in future patients. Two of the most extensively studied examples of this are the parotid dose response and its relationship to xerostomia (181), and the relationship between treatment-related dysphagia and dose to the larynx, pharynx, and pharyngeal constrictor muscles (182). These data have been previously discussed.

A comprehensive assessment of other issues related specifically to IMRT delivery was recently presented by Rosenthal et al (183). They specifically identified additional toxicities from IMRT that were not seen previously in the 3-field or conformal era. These included oral mucositis at unexpected sites, nausea from radiation alone and alopecia. These additional toxicities can be addressed by altering constraints in the dose-planning algorithm. We are clearly still on a learning curve with this technique in terms of defining the extent of its toxicity and the dose limits on certain structures. The distinct toxicity of IMRT delivery makes previously obtained information on fractionation and concurrent chemoradiotherapy that much more difficult to interpret.

Two other factors affect the current considerations of radiotherapy toxicity. First, the entire concept of toxicity has been undergoing a major rethinking. We are searching for reliable, reproducible ways to assess toxicity so that it can be more easily considered in the equation used to balance efficacy and morbidity of a given treatment approach. At present, there is huge variability in how toxicity data are scored, making comparisons difficult

(184). In addition, the current methods being used may not accurately assess the toxicity burden. The standard way to score toxicity has been to record the maximum toxicity a patient experiences. However, this method does not assess the full impact of the toxicity and can grossly underestimate the burden of an aggressive course of treatment. This may give a false impression when one is balancing the risk-benefit ratio of an apparently better treatment combination. A more accurate measure may be obtained by factoring in the duration of the toxicity at a given level—a type of “toxicity under the curve” measure (185). This recent proposal for a new toxicity assessment tool estimates that up to 29% to 70% of adverse events were excluded if the “standard” maximum grade method is used (185). Second, as a group, head and neck patients are now living longer than those treated in prior eras. As a result, long-term toxicity and quality-of-life parameters take on greater importance. In part, this has been influenced by the changing biology of the disease with the growing number of younger, HPV-positive patients in the SCCHN population. This epidemiologic shift has increased the focus on incorporating toxicity considerations into treatment decisions. In parallel with the alternative metrics used, radiation-based studies are now integrating quality-of-life tools much more frequently.

■ CONCLUSIONS

Current State of the Art

Radiotherapy of SCCHN in 2010 has reached an exciting point in its development. Significant progress has been made in the detailed methods to identify and delineate the multiple radiation targets that require treatment. Axial treatment planning images form the basis for identifying targets, using information gained from standard imaging modalities including CT, PET-CT, and MRI, as well as that gleaned from physical examination. The conceptual basis for what needs to be treated has evolved from the simple targets identified by bony anatomy on lateral radiographs to exquisitely

complicated and precisely identified at-risk structures in 3 dimensions. The radiation oncologist has multiple tools available to achieve highly conformal dose distributions as directed by the target delineation. IMRT is certainly the current standard of care for dose delivery and achieves these dose distributions by a combination of inverse planning and the use of MLCs to dynamically shape the beam confluence. There is a wealth of data on the required dose-volume relationships for tumor treatment, and the tolerance doses for critical normal tissue structures. This information is essential for designing a radiation plan that optimizes therapeutic ratio and minimizes long-term consequences of radiation-based treatment.

Future of Radiation-Based Treatment of SCCHN

One area being investigated is improvement of dose delivery. On some level we are likely approaching the limit of how much imaging can resolve distinctions in tumor physiology and anatomy, and how tightly radiation dose can be differentially delivered. Image guidance is an area that can add another level of precision on patient localization, but pushing much farther in terms of conformality may be self-defeating and increase the chances of missing a target. The anatomy of the head and neck has many intrinsic degrees of freedom, and some of the structures have intrinsic motility/mobility related to tongue motion, swallowing and breathing, and thus radiation planning will always have to consider this degree of irreproducibility. There does remain the potential for improvement of dose distribution, particularly in terms of normal tissue sparing with the use of protons, related types of particles, and axial methods of radiation delivery. Another of the ongoing challenges is finding the right formula for incorporating the chemoradiotherapy and radiation fractionation data acquired through many years of study with 3-field technique to the current dose painting approaches common with IMRT.

One of the areas with the greatest potential for improvement is in the accurate identification of microscopic disease and the effect this information would have on radiation targeting. There is a great deal of interest in “molecular imaging” which can improve radiation treatment in 2 critical areas. First, as the sensitivity of the imaging improves, we will be better able to identify where tumor and “microscopic” tumor may be present, perhaps having a reliable mechanism for identifying processes such as submucosal spread. This will add to the current imaging modalities and clinical exam to give a more accurate localization of targets. In addition, the functional assessment of tumors may improve treatment targeting with more resistant areas of a tumor (e.g., hypoxic, or less apoptosis prone regions) receiving a higher dose.

Another area of potential growth and improvement is in the further use of sensitizers and concurrent systemic agents. Radiation therapy remains the central component of nonsurgical management of SCCHN, but the most successful treatments involve a combination of radiotherapy with systemic therapy. Further progress in cytotoxic therapies, sensitizers, and targeted agents offers perhaps the greatest opportunity to further improve the treatment.

REFERENCES

1. Baker GR. Localization: conventional and CT simulation. *Br J Radiol.* 2006;79(Spec No 1):S36–S49.
2. Khan F. *The Physics of Radiation Therapy*. 3th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003:560.
3. Purdy JA. Current ICRU definitions of volumes: limitations and future directions. *Semin Radiat Oncol.* 2004;14(1):27–40.
4. Mah D, Chen CC. Image guidance in radiation oncology treatment planning: the role of imaging technologies on the planning process. *Semin Nucl Med.* 2008;38(2):114–118.
5. Goitein M. Future prospects in planning radiation therapy. *Cancer.* 1985;55(9 Suppl):2234–2239.
6. Gunderson LL, Tepper JE. *Clinical Radiation Oncology*. 1st ed. Philadelphia, PA: Churchill Livingstone; 1296.
7. Mukherji SK, Toledano AY, Beldon C, et al. Interobserver reliability of computed tomography-derived primary tumor volume measurement in patients with supraglottic carcinoma. *Cancer.* 2005;103:2616–2622.
8. Cooper JS, Mukherji SK, Toledano AY, et al. An evaluation of the variability of tumor-shape definition derived by experienced observers from CT images of supraglottic carcinomas (ACRIN protocol 6658). *Int J Radiat Oncol Biol Phys.* 2007;67:972–975.
9. Hoorweg JJ, Kruijt RH, Heijboer RJ, Eijkemans MJ, Kerrebijn JD. Reliability of interpretation of CT examination of the larynx in patients with glottic laryngeal carcinoma. *Otolaryngol Head Neck Surg.* 2006;135:129–134.
10. Chung NN, Ting LL, Hsu WC, Lui LT, Wang PM. Impact of magnetic resonance imaging versus CT on nasopharyngeal carcinoma: primary tumor target delineation for radiotherapy. *Head Neck.* 2004;26:241–246.
11. Chang JT, Lin CY, Chen TM, et al. Nasopharyngeal carcinoma with cranial nerve palsy: the importance of MRI for radiotherapy. *Int J Radiat Oncol Biol Phys.* 2005;63:1354–1360.
12. Rasch C, Keus R, Pameijer FA, et al. The potential impact of CT-MRI matching on tumor volume delineation in advanced head and neck cancer. *Int J Radiat Oncol Biol Phys.* 1997;39:841–848.
13. Gardner M, Halimi P, Valint D, et al. Use of single MRI and 18F-FDG PET-CT scans in both diagnosis and radiotherapy treatment planning in patients with head and neck cancer: advantage on target volume and critical organ delineation. *Head Neck.* 2009;31:461–467.
14. Daisne JF, Duprez T, Weynand B, et al. Tumor volume in pharyngolaryngeal squamous cell carcinoma: comparison at CT, MR imaging, and FDG PET and validation with surgical specimen. *Radiology.* 2004;233:93–100.
15. Adams S, Baum RP, Stuckensen T, Bitter K, Hör G. Prospective comparison of 18F-FDG PET with conventional imaging modalities (CT, MRI, US) in lymph node staging of head and neck cancer. *Eur J Nucl Med.* 1998;25:1255–1260.
16. Yoon DY, Hwang HS, Chang SK, et al. CT, MR, US, 18F-FDG PET/CT, and their combined use for the assessment of cervical lymph node metastases in squamous cell carcinoma of the head and neck. *Eur Radiol.* 2009;19:634–642.
17. Akoğlu E, Dutipek M, Bekiş R, Değirmenci B, Ada E, Güneri A. Assessment of cervical lymph node metastasis with different imaging methods in patients with head and neck squamous cell carcinoma. *J Otolaryngol.* 2005;34:384–394.
18. van den Brekel MW. Lymph node metastases: CT and MRI. *Eur J Radiol.* 2000;33(3):230–238.

19. King AD, Tse GM, Yuen EH, et al. Comparison of CT and MR imaging for the detection of extranodal neoplastic spread in metastatic neck nodes. *Eur J Radiol.* 2004;52:264–270.
20. Curtin HD, Ishwaran H, Mancuso AA, Dalley RW, Caudry DJ, McNeil BJ et al. Comparison of CT and MR imaging in staging of neck metastases. *Radiology.* 1998;207:123–130.
21. Juweid ME, Cheson BD. Positron-emission tomography and assessment of cancer therapy. *N Engl J Med.* 2006;354(5):496–507.
22. Schoder H, Ong SC. Fundamentals of molecular imaging: rationale and applications with relevance for radiation oncology. *Semin Nucl Med.* 2008;38(2):119–128.
23. Ahn PH, Garg MK. Positron emission tomography/computed tomography for target delineation in head and neck cancers. *Semin Nucl Med.* 2008;38(2):141–148.
24. Ashamalla H, Guirgus A, Bieniek E, et al. The impact of positron emission tomography/computed tomography in edge delineation of gross tumor volume for head and neck cancers. *Int J Radiat Oncol Biol Phys.* 2007;68:388–395.
25. Schwartz DL, Ford E, Rajendran J, et al. FDG-PET/CT imaging for preradiotherapy staging of head-and-neck squamous cell carcinoma. *Int J Radiat Oncol Biol Phys.* 2005;61:129–136.
26. Murakami R, Uozumi H, Hirai T, et al. Impact of FDG-PET/CT imaging on nodal staging for head-and-neck squamous cell carcinoma. *Int J Radiat Oncol Biol Phys.* 2007;68:377–382.
27. Ng SH, Yen TC, Liao CT, et al. 18F-FDG PET and CT/MRI in oral cavity squamous cell carcinoma: a prospective study of 124 patients with histologic correlation. *J Nucl Med.* 2005;46:1136–1143.
28. Ng SH, Yen TC, Chang JT, et al. Prospective study of [18F] fluorodeoxyglucose positron emission tomography and computed tomography and magnetic resonance imaging in oral cavity squamous cell carcinoma with palpably negative neck. *J Clin Oncol.* 2006;24:4371–4376.
29. Stoeckli SJ, Steinert H, Pfaltz M, Schmid S. Is there a role for positron emission tomography with 18F-fluorodeoxyglucose in the initial staging of nodal negative oral and oropharyngeal squamous cell carcinoma. *Head Neck.* 2002;24:345–349.
30. Schoder H, Carlson DL, Kraus DH, et al. 18F-FDG PET/CT for detecting nodal metastases in patients with oral cancer staged N0 by clinical examination and CT/MRI. *J Nucl Med.* 2006;47:755–762.
31. Wang D, Schultz CJ, Jursinic PA, et al. Initial experience of FDG-PET/CT guided IMRT of head-and-neck carcinoma. *Int J Radiat Oncol Biol Phys.* 2006;65:143–151.
32. Ciernik IF, Dizendorf E, Baumert BG, et al. Radiation treatment planning with an integrated positron emission and computer tomography (PET/CT): a feasibility study. *Int J Radiat Oncol Biol Phys.* 2003;57:853–863.
33. Schinagel DA, Hoffmann AL, Vogel WV, et al. Can FDG-PET assist in radiotherapy target volume definition of metastatic lymph nodes in head-and-neck cancer? *Radiother Oncol.* 2009;91:95–100.
34. Ireland RH, Dyker KE, Barber DC, et al. Nonrigid image registration for head and neck cancer radiotherapy treatment planning with PET/CT. *Int J Radiat Oncol Biol Phys.* 2007;68:952–957.
35. Hwang AB, Bacharach SL, Yom SS, et al. Can positron emission tomography (PET) or PET/Computed Tomography (CT) acquired in a nontreatment position be accurately registered to a head-and-neck radiotherapy planning CT? *Int J Radiat Oncol Biol Phys.* 2009;73:578–584.
36. Gionchetti P, Guarnieri C, Campieri M, et al. Scavenger effect of sulfasalazine, 5-aminosalicylic acid, and olsalazine on superoxide radical generation. *Dig Dis Sci.* 1991;36:174–178.
37. Lee N, Nehmeh S, Schoder H, et al. Prospective trial incorporating pre-/mid-treatment [18F]-misonidazole positron emission tomography for head-and-neck cancer patients undergoing concurrent chemoradiotherapy. *Int J Radiat Oncol Biol Phys.* 2009;75:101–108.
38. Lee NY, Mechalakos JG, Nehmeh S, et al. Fluorine-18-labeled fluoromisonidazole positron emission and computed tomography-guided intensity-modulated radiotherapy for head and neck cancer: a feasibility study. *Int J Radiat Oncol Biol Phys.* 2008;70:2–13.
39. Thorwarth D, Eschmann SM, Paulsen F, Alber M. Hypoxia dose painting by numbers: a planning study. *Int J Radiat Oncol Biol Phys.* 2007;68:291–300.
40. Chao KS, Bosch WR, Mutic S, et al. A novel approach to overcome hypoxic tumor resistance: Cu-ATSM-guided intensity-modulated radiation therapy. *Int J Radiat Oncol Biol Phys.* 2001;49:1171–1182.
41. Gregoire V, Coche E, Cosnard G, Hamoir M, Reyckel H. Selection and delineation of lymph node target volumes in head and neck conformal radiotherapy. Proposal for standardizing terminology and procedure based on the surgical experience. *Radiother Oncol.* 2000;56:135–150.
42. Nowak PJ, Wijers OB, Lagerwaard FJ, Levendag PC. A three-dimensional CT-based target definition for

- elective irradiation of the neck. *Int J Radiat Oncol Biol Phys*. 1999;45:33–39.
43. Wijers OB, Levendag PC, Tan T, et al. A simplified CT-based definition of the lymph node levels in the node negative neck. *Radiother Oncol*. 1999;52:35–42.
 44. Som, PM, Curtin HD, Mancuso AA. An imaging-based classification for the cervical nodes designed as an adjunct to recent clinically based nodal classifications. *Arch Otolaryngol Head Neck Surg*. 1999;125(4):388–396.
 45. Palazzi M, Soatti C, Bianchi E, et al. Guidelines for the delineation of nodal regions of the head and neck on axial computed tomography images. *Tumori*. 2002;88:355–360.
 46. Sanguineti G, Culp LR, Endres EJ, Bayouth JE. Are neck nodal volumes drawn on CT slices covered by standard three-field technique? *Int J Radiat Oncol Biol Phys*. 2004;59:725–742.
 47. Gregoire V, Levendag P, Ang KK, et al. CT-based delineation of lymph node levels and related CTVs in the node-negative neck: DAHANCA, EORTC, GORTEC, NCIC, RTOG consensus guidelines. *Radiother Oncol*. 2003;69:227–236.
 48. Langendijk JA, Doornaert P, Verdonck-de Leeuw IM, et al. Impact of late treatment-related toxicity on quality of life among patients with head and neck cancer treated with radiotherapy. *J Clin Oncol*. 2008;26:3770–3776.
 49. Mese H, Matsuo R. Salivary secretion, taste and hyposalivation. *J Oral Rehabil*. 2007;34(10):711–723.
 50. Eisbruch A, Ten Haken RK, Kim HM, Marsh LH, Ship JA. Dose, volume, and function relationships in parotid salivary glands following conformal and intensity-modulated irradiation of head and neck cancer. *Int J Radiat Oncol Biol Phys*. 1999;45:577–587.
 51. Li Y, et al. The impact of dose on parotid salivary recovery in head and neck cancer patients treated with radiation therapy. *Int J Radiat Oncol Biol Phys*. 2007;67:660–669.
 52. Jellema AP, Doornaert P, Slotman BJ, Leemans CR, Langendijk JA. Does radiation dose to the salivary glands and oral cavity predict patient-rated xerostomia and sticky saliva in head and neck cancer patients treated with curative radiotherapy? *Radiother Oncol*. 2005;77:164–171.
 53. Murdoch-Kinch CA, Kim HM, Vineberg KA, Ship JA, Eisbruch A. Dose-effect relationships for the submandibular salivary glands and implications for their sparing by intensity modulated radiotherapy. *Int J Radiat Oncol Biol Phys*. 2008;72:373–382.
 54. van Rij CM, Oughlane-Heemsbergen WD, Ackerstaff AH, et al. Parotid gland sparing IMRT for head and neck cancer improves xerostomia related quality of life. *Radiat Oncol*. 2008;3:41.
 55. Jabbari S, Kim HM, Feng M, et al. Matched case-control study of quality of life and xerostomia after intensity-modulated radiotherapy or standard radiotherapy for head-and-neck cancer: initial report. *Int J Radiat Oncol Biol Phys*. 2005;63:725–731.
 56. Garden AS, Harris J, Trotti A, et al. Long-term results of concomitant boost radiation plus concurrent cisplatin for advanced head and neck carcinomas: a phase II trial of the radiation therapy oncology group (RTOG 99-14). *Int J Radiat Oncol Biol Phys*. 2008;71:1351–1355.
 57. Rogers LQ, Rao K, Malone J, et al. Factors associated with quality of life in outpatients with head and neck cancer 6 months after diagnosis. *Head Neck*. 2009;31:1207–1214.
 58. Gurney TA, Eisele DW, Orloff LA, Wang SJ. Predictors of quality of life after treatment for oral cavity and oropharyngeal carcinoma. *Otolaryngol Head Neck Surg*. 2008;139:262–267.
 59. Caudell JJ, Schaner PE, Meredith RF, et al. Factors associated with long-term dysphagia after definitive radiotherapy for locally advanced head-and-neck cancer. *Int J Radiat Oncol Biol Phys*. 2009;73:410–415.
 60. Rosenthal DI, Lewin JS, Eisbruch A. Prevention and treatment of dysphagia and aspiration after chemoradiation for head and neck cancer. *J Clin Oncol*. 2006;24(17):2636–2643.
 61. Caglar HB, Tishler RB, Othus M, et al. Dose to larynx predicts for swallowing complications after intensity-modulated radiotherapy. *Int J Radiat Oncol Biol Phys*. 2008;72:1110–1118.
 62. Caudell JJ, Schaner PE, Desmond RA, Meredith RF, Spencer SA, Bonner JA. Dosimetric Factors Associated With Long-Term Dysphagia After Definitive Radiotherapy for Squamous Cell Carcinoma of the Head and Neck. *Int J Radiat Oncol Biol Phys*. 2010;76(2):403–409. Epub 2009 May 19.
 63. Feng FY, Kim HM, Lyden TH, et al. Intensity-modulated radiotherapy of head and neck cancer aiming to reduce dysphagia: early dose-effect relationships for the swallowing structures. *Int J Radiat Oncol Biol Phys*. 2007;68:1289–1298.
 64. Levendag PC, Teguh DN, Voet P, et al. Dysphagia disorders in patients with cancer of the oropharynx are significantly affected by the radiation therapy dose to the superior and middle constrictor muscle: a dose-effect relationship. *Radiother Oncol*. 2007;85:64–73.

65. Dirix P, Abbeel S, Vanstraelen B, Hermans R, Nuyts S. Dysphagia after chemoradiotherapy for head-and-neck squamous cell carcinoma: dose-effect relationships for the swallowing structures. *Int J Radiat Oncol Biol Phys.* 2009;75:385–392.
66. Glanzmann C, Gratz KW. Radionecrosis of the mandibula: a retrospective analysis of the incidence and risk factors. *Radiother Oncol.* 1995;36(2):94–100.
67. Lee AW, Kwong DL, Leung SF, et al. Factors affecting risk of symptomatic temporal lobe necrosis: significance of fractional dose and treatment time. *Int J Radiat Oncol Biol Phys.* 2002;53:75–85.
68. Jen YM, Hsu WL, Chen CY, et al. Different risks of symptomatic brain necrosis in NPC patients treated with different altered fractionated radiotherapy techniques. *Int J Radiat Oncol Biol Phys.* 2001;51:344–348.
69. Lee AW, Ng WT, Hung WM, et al. Major late toxicities after conformal radiotherapy for nasopharyngeal carcinoma-patient- and treatment-related risk factors. *Int J Radiat Oncol Biol Phys.* 2009;73:1121–1128.
70. Rosenblatt E, Brook OR, Erlich N, Miller B, Joachims HZ, Kuten A. Late visual and auditory toxicity of radiotherapy for nasopharyngeal carcinoma. *Tumori.* 2003;89:68–74.
71. Hazuka MB, Martel MK, Marsh L, Lichter AS, Wolf GT. Preservation of parotid function after external beam irradiation in head and neck cancer patients: a feasibility study using 3-dimensional treatment planning. *Int J Radiat Oncol Biol Phys.* 1993;27:731–737.
72. Eisbruch A, Ship JA, Martel MK, et al. Parotid gland sparing in patients undergoing bilateral head and neck irradiation: techniques and early results. *Int J Radiat Oncol Biol Phys.* 1996;36:469–480.
73. Chau RM, Teo PM, Choi PH, Cheung KY, Lee WY. Three-dimensional dosimetric evaluation of a conventional radiotherapy technique for treatment of nasopharyngeal carcinoma. *Radiother Oncol.* 2001;58:143–153.
74. Mendenhall WM, Amdur RJ, Palta JR. Intensity-modulated radiotherapy in the standard management of head and neck cancer: promises and pitfalls. *J Clin Oncol.* 2006;24(17):2618–2623.
75. Chau RM, Teo PM, Kam MK, Leung SF, Cheung KY, Chan AT. Dosimetric comparison between 2-dimensional radiation therapy and intensity modulated radiation therapy in treatment of advanced T-stage nasopharyngeal carcinoma: to treat less or more in the planning organ-at-risk volume of the brainstem and spinal cord. *Med Dosim.* 2007;32:263–270.
76. Xia P, Lee N, Liu YM, et al. A study of planning dose constraints for treatment of nasopharyngeal carcinoma using a commercial inverse treatment planning system. *Int J Radiat Oncol Biol Phys.* 2004;59:886–896.
77. Penagaricano JA, Ratanatharathorn V, Papanikolaou N, Yan Y. Intensity-modulated radiation therapy reduces the dose to normal tissue in T2N0M0 squamous cell carcinoma of the glottic larynx. *Med Dosim.* 2004;29:254–257.
78. Johansson J, Blomquist E, Montelius A, Isacson U, Glimelius B. Potential outcomes of modalities and techniques in radiotherapy for patients with hypopharyngeal carcinoma. *Radiother Oncol.* 2004;72:129–138.
79. Clark CH, Bidmead AM, Mubata CD, Harrington KJ, Nutting CM. Intensity-modulated radiotherapy improves target coverage, spinal cord sparing and allows dose escalation in patients with locally advanced cancer of the larynx. *Radiother Oncol.* 2004;70:189–198.
80. Lee N, Puri DR, Blanco AI, Chao KS. Intensity-modulated radiation therapy in head and neck cancers: an update. *Head Neck.* 2007;29:387–400.
81. Rosenthal DI, Chambers MS, Fuller CD, et al. Beam path toxicities to non-target structures during intensity-modulated radiation therapy for head and neck cancer. *Int J Radiat Oncol Biol Phys.* 2008;72:747–755.
82. Amdur RJ, Li JG, Liu C, Hinerman RW, Mendenhall WM. Unnecessary laryngeal irradiation in the IMRT era. *Head Neck.* 2004;26:257–263. (discussion 263–254).
83. Amdur RJ, Liu C, Li J, Mendenhall W, Hinerman R. Matching intensity-modulated radiation therapy to an anterior low neck field. *Int J Radiat Oncol Biol Phys.* 2007;69:S46–S48.
84. Hall EJ. Intensity-modulated radiation therapy, protons, and the risk of second cancers. *Int J Radiat Oncol Biol Phys.* 2006;65:1–7.
85. Hall EJ, Wu CS. Radiation-induced second cancers: the impact of 3D-CRT and IMRT. *Int J Radiat Oncol Biol Phys.* 2003;56:83–88.
86. Ruben JD, Davis S, Evans C, et al. The effect of intensity-modulated radiotherapy on radiation-induced second malignancies. *Int J Radiat Oncol Biol Phys.* 2008;70:1530–1536.
87. Verellen D, Vanhavere F. Risk assessment of radiation-induced malignancies based on whole-body equivalent dose estimates for IMRT treatment in the head and neck region. *Radiother Oncol.* 1999;53:199–203.
88. Rades D, Fehlauer F, Wroblewski J, Albers D, Schild SE, Schmitt R. Prognostic factors in head-and-neck cancer patients treated with surgery followed by

- intensity-modulated radiotherapy (IMRT), 3D-conformal radiotherapy, or conventional radiotherapy. *Oral Oncol.* 2007;43:535–543.
89. Graff P, Lapeyre M, Desandes E, et al. Impact of intensity-modulated radiotherapy on health-related quality of life for head and neck cancer patients: matched-pair comparison with conventional radiotherapy. *Int J Radiat Oncol Biol Phys.* 2007;67:1309–1317.
 90. Lee NY, de Arruda FF, Puri DR, et al. A comparison of intensity-modulated radiation therapy and concomitant boost radiotherapy in the setting of concurrent chemotherapy for locally advanced oropharyngeal carcinoma. *Int J Radiat Oncol Biol Phys.* 2006;66: 966–974.
 91. Chao KS, Ozyigit G, Blanco AI, et al. Intensity-modulated radiation therapy for oropharyngeal carcinoma: impact of tumor volume. *Int J Radiat Oncol Biol Phys.* 2004;59:43–50.
 92. Huang K, Xia P, Chuang C, et al. Intensity-modulated chemoradiation for treatment of stage III and IV oropharyngeal carcinoma: the University of California-San Francisco experience. *Cancer.* 2008;113:497–507.
 93. Garden AS, Morrison WH, Wong PF, et al. Disease-control rates following intensity-modulated radiation therapy for small primary oropharyngeal carcinoma. *Int J Radiat Oncol Biol Phys.* 2007;67:438–444.
 94. de Arruda FF, Puri DR, Zhung J, et al. Intensity-modulated radiation therapy for the treatment of oropharyngeal carcinoma: the Memorial Sloan-Kettering Cancer Center experience. *Int J Radiat Oncol Biol Phys.* 2006;64:363–373.
 95. Daly ME, Le QT, Maxim PG, et al. Intensity-modulated radiotherapy in the treatment of oropharyngeal cancer: clinical outcomes and patterns of failure. *Int J Radiat Oncol Biol Phys.* 2010;76(5):1339–1346. (Epub 2009 Jun 18).
 96. Lee N, Xia P, Quivey JM, et al. Intensity-modulated radiotherapy in the treatment of nasopharyngeal carcinoma: an update of the UCSF experience. *Int J Radiat Oncol Biol Phys.* 2002;53:12–22.
 97. Kwong DL, Pow EH, Sham JS, et al. Intensity-modulated radiotherapy for early-stage nasopharyngeal carcinoma: a prospective study on disease control and preservation of salivary function. *Cancer.* 2004;101:1584–1593.
 98. Lin S, Pan J, Han L, Zhang X, Liao X, Lu JJ. Nasopharyngeal Carcinoma Treated with Reduced-Volume Intensity-Modulated Radiation Therapy: Report on the 3-Year Outcome of a Prospective Series. *Int J Radiat Oncol Biol Phys.* 2009;75(4):1071–1078. (Epub 2009 Apr 11).
 99. Cannon DM, Lee NY. Recurrence in region of spared parotid gland after definitive intensity-modulated radiotherapy for head and neck cancer. *Int J Radiat Oncol Biol Phys.* 2008;70(3):660–665.
 100. Chao KS, Ozyigit G, Tran BN, Cengiz M, Dempsey JE, Low DA. Patterns of failure in patients receiving definitive and postoperative IMRT for head-and-neck cancer. *Int J Radiat Oncol Biol Phys.* 2003;55:312–321.
 101. Lee N, Harris J, Garden AS, et al. Intensity-modulated radiation therapy with or without chemotherapy for nasopharyngeal carcinoma: radiation therapy oncology group phase II trial 0225. *J Clin Oncol.* 2009;27:3684–3690.
 102. Eisbruch A, Harris J, Garden AS, et al. Multi-institutional trial of accelerated hypofractionated intensity-modulated radiation therapy for early-stage oropharyngeal cancer (RTOG 00-22). *Int J Radiat Oncol Biol Phys.* 2010;76(5):1333–1338. (Epub 2009 Jun 18).
 103. Kam MK, Leung SF, Zee B, et al. Prospective randomized study of intensity-modulated radiotherapy on salivary gland function in early-stage nasopharyngeal carcinoma patients. *J Clin Oncol.* 2007;25:4873–4879.
 104. Clark CH, Miles EA, Urbano MT, et al. Pre-trial quality assurance processes for an intensity-modulated radiation therapy (IMRT) trial: PARSPORT, a UK multicentre Phase III trial comparing conventional radiotherapy and parotid-sparing IMRT for locally advanced head and neck cancer. *Br J Radiol.* 2009;82:585–594.
 105. Nutting CM, A'hern A, Rogers MS, et al. First results of a phase III multicenter randomized controlled trial of intensity modulated (IMRT) versus conventional radiotherapy (RT) in head and neck cancer (PARSPORT: ISRCTN48243537; CRUK/03/005). *J Clin Oncol.* 2009;27:LBA6006.
 106. Longobardi B, De Martin E, Fiorino C, et al. Comparing 3DCRT and inversely optimized IMRT planning for head and neck cancer: equivalence between step-and-shoot and sliding window techniques. *Radiother Oncol.* 2005;77:148–156.
 107. Nicolini G, Fogliata A, Cozzi L. IMRT with the sliding window: comparison of the static and dynamic methods. Dosimetric and spectral analysis. *Radiother Oncol.* 2005;75(1):112–119.
 108. Verbakel WF, Cuijpers JB, Hoffmans D, et al. Volumetric intensity-modulated arc therapy vs. conventional IMRT in head-and-neck cancer: a comparative planning and dosimetric study. *Int J Radiat Oncol Biol Phys.* 2009;74:252–259.
 109. Beavis AW. Is tomotherapy the future of IMRT? *Br J Radiol.* 2004;77(916):285–295.

110. Sheng K, Molloy JA, Read PW. Intensity-modulated radiation therapy (IMRT) dosimetry of the head and neck: a comparison of treatment plans using linear accelerator-based IMRT and helical tomotherapy. *Int J Radiat Oncol Biol Phys*. 2006;65(3):917–923.
111. Cao D, Holmes TW, Afghan MK, Shepard DM. Comparison of plan quality provided by intensity-modulated arc therapy and helical tomotherapy. *Int J Radiat Oncol Biol Phys*. 2007;69:240–250.
112. Wolff D, Stieler F, Welzel G, et al. Volumetric modulated arc therapy (VMAT) vs. serial tomotherapy, step-and-shoot IMRT and 3D-conformal RT for treatment of prostate cancer. *Radiother Oncol*. 2009 Nov;93(2):226–233. (Epub 2009 Sep 16).
113. Astreinidou E, Bel A, Raaijmakers CP, Terhaard CH, Lagendijk JJ. Adequate margins for random setup uncertainties in head-and-neck IMRT. *Int J Radiat Oncol Biol Phys* 2005;61:938–944.
114. Hong TS, Tome WA, Chappell RJ, Chinnaiyan P, Mehta MP, Harari PM. The impact of daily setup variations on head-and-neck intensity-modulated radiation therapy. *Int J Radiat Oncol Biol Phys*. 2005;61: 779–788.
115. Bentel GC, Marks LB, Hendren K, Brizel DM. Comparison of two head and neck immobilization systems. *Int J Radiat Oncol Biol Phys*. 1997;38:867–873.
116. Thornton AF, Jr, Ten Haken RK, Gerhardtson A, Correll M. Three-dimensional motion analysis of an improved head immobilization system for simulation, CT, MRI, and PET imaging. *Radiother Oncol*. 1991;20:224–228.
117. Gilbeau L, Octave-Prignot M, Loncol T, Renard L, Scalliet P, Grégoire V. Comparison of setup accuracy of three different thermoplastic masks for the treatment of brain and head and neck tumors. *Radiother Oncol*. 2001;58:155–162.
118. Court LE, Wolfsberger L, Allen AM, James S, Tishler RB. Clinical experience of the importance of daily portal imaging for head and neck IMRT treatments. *J Appl Clin Med Phys*. 2008;9:2756.
119. Nath SK, Simpson DR, Rose BS, Sandhu AP. Recent advances in image-guided radiotherapy for head and neck carcinoma. *J Oncol*. 2009;7521–7535.
120. Dawson LA, Jaffray DA. Advances in image-guided radiation therapy. *J Clin Oncol*. 2007;25:938–946.
121. Pisani L, Lockman D, Jaffray D, Martinez A, Wong J. Setup error in radiotherapy: on-line correction using electronic kilovoltage and megavoltage radiographs. *Int J Radiat Oncol Biol Phys*. 2000;47:825–839.
122. Court L, Rosen I, Mohan R, Dong L. Evaluation of mechanical precision and alignment uncertainties for an integrated CT/LINAC system. *Med Phys*. 2003;30:1198–1210.
123. Den RB, Doemer A, Kubicek G, et al. Daily image guidance with cone-beam computed tomography for head-and-neck cancer intensity-modulated radiotherapy: a prospective study. *Int J Radiat Oncol Biol Phys*. 2010;76(5):1353–1359. (Epub 2009 Jun 18).
124. van Kranen S, van Beek S, Rasch C, van Herk M, Sonke JJ. Setup uncertainties of anatomical subregions in head-and-neck cancer patients after offline CBCT guidance. *Int J Radiat Oncol Biol Phys*. 2009;73:1566–1573.
125. Polat B, Wilbert J, Baier K, Flentje M, Guckenberger M. Nonrigid patient setup errors in the head-and-neck region. *Strahlenther Onkol*. 2007;183: 506–511.
126. Barker JL, Jr, Garden AS, Ang KK, et al. Quantification of volumetric and geometric changes occurring during fractionated radiotherapy for head-and-neck cancer using an integrated CT/linear accelerator system. *Int J Radiat Oncol Biol Phys*. 2004;59:960–970.
127. O'Daniel JC, Garden AS, Schwartz DL, et al. Parotid gland dose in intensity-modulated radiotherapy for head and neck cancer: is what you plan what you get? *Int J Radiat Oncol Biol Phys*. 2007;69:1290–1296.
128. Hansen EK, Bucci MK, Quivey JM, Weinberg V, Xia P. Repeat CT imaging and replanning during the course of IMRT for head-and-neck cancer. *Int J Radiat Oncol Biol Phys*. 2006;64:355–362.
129. Kuo YC, Wu TH, Chung TS, et al. Effect of regression of enlarged neck lymph nodes on radiation doses received by parotid glands during intensity-modulated radiotherapy for head and neck cancer. *Am J Clin Oncol*. 2006;29:600–605.
130. Laramore GE. Role of particle radiotherapy in the management of head and neck cancer. *Curr Opin Oncol*. 2009;21:224–231.
131. Maor MH, Errington RD, Caplan RJ, et al. Fast-neutron therapy in advanced head and neck cancer: a collaborative international randomized trial. *Int J Radiat Oncol Biol Phys*. 1995;32:599–604.
132. Griffin TW, Davis R, Laramore GE, et al. Fast neutron irradiation of metastatic cervical adenopathy: the results of a randomized RTOG study. *Int J Radiat Oncol Biol Phys*. 1983;9:1267–1270.
133. Griffin TW, Pajak TF, Maor MH, et al. Mixed neutron/photon irradiation of unresectable squamous cell carcinomas of the head and neck: the final report of a randomized cooperative trial. *Int J Radiat Oncol Biol Phys*. 1989;17:9592965.
134. Laramore GE, Krall JM, Griffin TW, et al. Neutron versus photon irradiation for unresectable salivary

- gland tumors: final report of an RTOG-MRC randomized clinical trial. Radiation Therapy Oncology Group. Medical Research Council. *Int J Radiat Oncol Biol Phys.* 1993;27:235–240.
135. Jereczek-Fossa BA, Krenegli M, Orecchia R. Particle beam radiotherapy for head and neck tumors: radiobiological basis and clinical experience. *Head Neck.* 2006;28(8):750–760.
 136. Chan AW, Liebsch NJ. Proton radiation therapy for head and neck cancer. *J Surg Oncol.* 2008;97(8):697–700.
 137. Thorwarth D, Soukup M, Alber M. Dose painting with IMPT, helical tomotherapy and IMXT: a dosimetric comparison. *Radiother Oncol.* 2008;86(1):30–34.
 138. Steneker M, Lomax A, Schneider U. Intensity modulated photon and proton therapy for the treatment of head and neck tumors. *Radiother Oncol.* 2006;80(2):263–267.
 139. Arjomandy B, Sahoo N, Cox J, Lee A, Gillin M. Comparison of surface doses from spot scanning and passively scattered proton therapy beams. *Phys Med Biol.* 2009;54:N295–N302.
 140. Titt U, Zheng Y, Vassiliev ON, Newhauser WD. Monte Carlo investigation of collimator scatter of proton-therapy beams produced using the passive scattering method. *Phys Med Biol.* 2008;53:487–504.
 141. Goitein M. Magical protons? *Int J Radiat Oncol Biol Phys.* 2008;70:654–656.
 142. Andreo P. On the clinical spatial resolution achievable with protons and heavier charged particle radiotherapy beams. *Phys Med Biol.* 2009;54:N205–N215.
 143. Schneider U, Lomax A, Hauser B, Kaser-Hotz B. Is the risk for secondary cancers after proton therapy enhanced distal to the Planning Target Volume? A two-case report with possible explanations. *Radiat Environ Biophys.* 2006;45:39–43.
 144. Slater JD, Yonemoto LT, Mantik DW, et al. Proton radiation for treatment of cancer of the oropharynx: early experience at Loma Linda University Medical Center using a concomitant boost technique. *Int J Radiat Oncol Biol Phys.* 2005;62:494–500.
 145. Hall EJ, Giaccia AJ. *Radiobiology for the Radiologist.* New York, NY: Lippincott Williams & Wilkins; 2005.
 146. Bourhis J, Overgaard J, Audry H, et al. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. *Lancet.* 2006;368(9538):843–854.
 147. Horiot JC, Le Fur R, N'Guyen T, et al. Hyperfractionation versus conventional fractionation in oropharyngeal carcinoma: final analysis of a randomized trial of the EORTC cooperative group of radiotherapy. *Radiother Oncol.* 1992;(4):231–241.
 148. Horiot JC, Bontemps P, van den Bogaert W, et al. Accelerated fractionation (AF) compared to conventional fractionation (CF) improves loco-regional control in the radiotherapy of advanced head and neck cancers: results of the EORTC 22851 randomized trial. *Radiother Oncol.* 1997;(2):111–121.
 149. Pinto LH, Canary PC, Araújo CM, Bacelar SC, Souhami L. Prospective randomized trial comparing hyperfractionated versus conventional radiotherapy in stages III and IV oropharyngeal carcinoma. *Int J Radiat Oncol Biol Phys.* 1991;(3):557–562.
 150. Fu KK, Pajak TF, Trotti A, et al. A Radiation Therapy Oncology Group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: first report of RTOG 9003. *Int J Radiat Oncol Biol Phys.* 2000;48(1):7–16.
 151. Bourhis J, Overgaard J, Audry H, et al. Meta-Analysis of Radiotherapy in Carcinomas of Head and neck (MARCH) Collaborative Group. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. *Lancet.* 2006;368(9538):843–854. Review.
 152. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med.* 2006;354(6):567–578.
 153. Adelstein DJ, Li Y, Adams GL, et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. *J Clin Oncol.* 2003;21(1):92–98.
 154. Brizel DM, Esclamado R. Concurrent chemoradiotherapy for locally advanced, nonmetastatic, squamous carcinoma of the head and neck: consensus, controversy, and conundrum. *J Clin Oncol.* 2006;24(17):2612–2617.
 155. Staar S, Rudat V, Stuetzer H, et al. Intensified hyperfractionated accelerated radiotherapy limits the additional benefit of simultaneous chemotherapy—results of a multicentric randomized German trial in advanced head-and-neck cancer. *Int J Radiat Oncol Biol Phys.* 2001;50(5):1161–1171.
 156. Brizel DM, Albers ME, Fisher SR, et al. Hyperfractionated irradiation with or without concurrent chemotherapy for locally advanced head and neck cancer. *N Engl J Med.* 1998;338(25):1798–1804.
 157. Ang K, Pajak T, Wheeler R, et al. Phase III Trial To Test Accelerated Versus Standard Fractionation In Combination With Concurrent Cisplatin For Head And Neck Carcinomas (rtog 0129): Report Of Efficacy And Toxicity. Abstract LB2. ASTRO, 2009, Chicago, IL.

158. Orlandi E, Palazzi M, Pignoli E, Fallai C, Giostra A, Olmi P. Radiobiological basis and clinical results of the simultaneous integrated boost (SIB) in intensity modulated radiotherapy (IMRT) for head and neck cancer: a review. *Crit Rev Oncol Hematol*. 2010;73(2):111–125.
159. Ho KF, Fowler JF, Sykes AJ, Yap BK, Lee LW, Slevin NJ. IMRT dose fractionation for head and neck cancer: variation in current approaches will make standardisation difficult. *Acta Oncol*. 2009;48(3):431–439.
160. Schwartz M, Vuong T, Ballivy O, Parker W, Patrocinio H. Accelerated radiotherapy with simultaneous integrated boost fractionation and intensity-modulated radiotherapy for advanced head and neck cancer. *Otolaryngol Head Neck Surg*. 2007;136(4):549–555.
161. Overgaard J, Hansen HS, Specht L, et al. Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck: DAHANCA 6 and 7 randomised controlled trial. *Lancet*. 2003;362(9388):933–940.
162. Chua DT, Sham JS, Kwong PW, Hung KN, Leung LH. Linear accelerator-based stereotactic radiosurgery for limited, locally persistent, and recurrent nasopharyngeal carcinoma: efficacy and complications. *Int J Radiat Oncol Biol Phys*. 2003;56(1):177–183.
163. Roh KW, Jang JS, Kim MS, et al. Fractionated stereotactic radiotherapy as reirradiation for locally recurrent head and neck cancer. *Int J Radiat Oncol Biol Phys*. 2009;74(5):1348–1355. (Epub 2008 Dec 29).
164. Rosenthal DI, Asper JA, Barker JL Jr, et al. Importance of patient examination to clinical quality assurance in head and neck radiation oncology. *Head Neck*. 2006;28(11):967–973.
165. Bernier J, Domenge C, Ozsahin M, et al. European Organization for research and treatment of cancer trial 22931. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med*. 2004;350(19):1945–1952.
166. Cooper JS, Pajak TF, Forastiere AA, et al. Radiation Therapy Oncology Group 9501/Intergroup. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *N Engl J Med*. 2004;350(19):1937–1944.
167. Kies MS, Harris J, Rotman MZ, et al. Phase II Randomized Trial of Postoperative Chemoradiation Plus Cetuximab for High-Risk Squamous Cell Carcinoma of the Head and Neck (RTOG 0234). Abstract #29 ASTRO, 2009, Chicago, IL.
168. Grégoire V, Eisbruch A, Hamoir M, Levendag P. Proposal for the delineation of the nodal CTV in the node-positive and the post-operative neck. *Radiother Oncol*. 2006;79(1):15–20.
169. Rades D, Fehlaue F, Wroblewski J, Albers D, Schild SE, Schmidt R. Prognostic factors in head-and-neck cancer patients treated with surgery followed by intensity-modulated radiotherapy (IMRT), 3D-conformal radiotherapy, or conventional radiotherapy. *Oral Oncol*. 2007;43(6):535–543. (Epub 2006 Sep 26).
170. Studer G, Furrer K, Davis BJ, et al. Postoperative IMRT in head and neck cancer. *Radiat Oncol*. 2006;1:40.
171. Pehlivan B, Luthi F, Matzinger O, et al. Feasibility and efficacy of accelerated weekly concomitant boost postoperative radiation therapy combined with concomitant chemotherapy in patients with locally advanced head and neck cancer. *Ann Surg Oncol*. 2009;16(5):1337–1343. (Epub 2009 Mar 12).
172. Studer G, Zwahlen RA, Graetz KW, Davis BJ, Glanzmann C. IMRT in oral cavity cancer. *Radiat Oncol*. 2007;2:16.
173. Yao M, Chang K, Funk GF, et al. The failure patterns of oral cavity squamous cell carcinoma after intensity-modulated radiotherapy-the university of iowa experience. *Int J Radiat Oncol Biol Phys*. 2007;67(5):1332–1341. (Epub 2007 Feb 2).
174. Gomez DR, Zhung JE, Gomez J, et al. Intensity-modulated radiotherapy in postoperative treatment of oral cavity cancers. *Int J Radiat Oncol Biol Phys*. 2009;73(4):1096–1103. (Epub 2008 Aug 15).
175. Chen WC, Hwang TZ, Wang WH, et al. Comparison between conventional and intensity-modulated post-operative radiotherapy for stage III and IV oral cavity cancer in terms of treatment results and toxicity. *Oral Oncol*. 2009;45(6):505–510. (Epub 2008 Sep 19).
176. Salama JK, Haddad RI, Kies MS, et al. Clinical practice guidance for radiotherapy planning after induction chemotherapy in locoregionally advanced head-and-neck cancer. *Int J Radiat Oncol Biol Phys*. 2009;75(3):725–733.
177. Spaulding MB, Fischer SG, Wolf GT. Tumor response, toxicity, and survival after neoadjuvant organ-preserving chemotherapy for advanced laryngeal carcinoma. The Department of Veterans Affairs Cooperative Laryngeal Cancer Study Group. *J Clin Oncol*. 1994;12(8):1592–1599.
178. The Department of Veterans Affairs Laryngeal Cancer Study Group. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. *N Engl J Med*. 1991;324(24):1685–1690.

179. Sanguineti G, Endres EJ, Gunn BG, Parker B. Is there a “mucosa-sparing” benefit of IMRT for head-and-neck cancer? *Int J Radiat Oncol Biol Phys.* 2006;66(3):931–938.
180. Monroe AT, Reddy SC, Gibbs GL, White GA, Peddada AV. Factors associated with radiation-induced nausea and vomiting in head and neck cancer patients treated with intensity modulated radiation therapy. *Radiother Oncol.* 2008;87(2):188–194. (Epub 2008 Jan 30).
181. Li Y, Taylor JM, Ten Haken RK, Eisbruch A. The impact of dose on parotid salivary recovery in head and neck cancer patients treated with radiation therapy. *Int J Radiat Oncol Biol Phys.* 2007;67(3):660–669. (Epub 2006 Dec 4).
182. Caglar HB, Tishler RB, Othus M, et al. Dose to larynx predicts for swallowing complications after intensity-modulated radiotherapy. *Int J Radiat Oncol Biol Phys.* 2008;72(4):1110–1118. (Epub 2008 May 28).
183. Rosenthal DI, Chambers MS, Fuller CD, et al. Beam path toxicities to non-target structures during intensity-modulated radiation therapy for head and neck cancer. *Int J Radiat Oncol Biol Phys.* 2008;72(3):747–755. (Epub 2008 May 1).
184. Davidson SE, Trotti A, Ataman OU, et al. Improving the capture of adverse event data in clinical trials: the role of the International Atomic Energy Agency. *Int J Radiat Oncol Biol Phys.* 2007;69(4):1218–1221. (Epub 2007 Aug 6).
185. Trotti A, Pajak TF, Gwede CK, et al. TAME: development of a new method for summarising adverse events of cancer treatment by the Radiation Therapy Oncology Group. *Lancet Oncol.* 2007;8(7):613–624.

CHAPTER 3

Molecularly Targeted Agents in Recurrent, Metastatic Squamous Cell Carcinoma of the Head and Neck

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■ INTRODUCTION

Head and neck cancer is the fifth most common cancer in the world. In the United States, it accounts for 3% to 5% of all malignancies annually, representing approximately 2% of all cancer deaths in 2009 (1). Despite decades of research, therapeutic options are limited for patients who have recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN), and most patients will die within 1 year of recurrence (2). The most active cytotoxic regimens include a platinum agent in combination with fluorouracil or a taxane and have been associated with a 30% response rate, a 3- to 4-month median progression-free survival, and a median overall survival of 6 to 8 months (2,3). Patients progressing on a platinum-based therapy have limited treatment options and poor prognosis. Few patients with recurrent disease are suitable for potentially curative salvage surgery, and some patients can benefit from radiation with or without chemotherapy, with a dismal overall response to second-line therapy. In addition, radiation, salvage surgery, and chemotherapy have a high toxicity profile and should be carefully planned in the palliative setting (4). Not

surprisingly, tumor-specific approaches have been studied in this setting, and it is hoped that molecularly targeted agents will fulfill this gap both in the efficacy and toxicity.

Increased understanding of the biology of cancer and the availability of new technologies, such as microarrays, proteomics, and novel imaging, has allowed the identification of molecular targets for cancer drug development. Early in the decade, Hanahan and Weinberg (5) described the hallmarks of cancer as being self-sufficiency in growth signals, insensitivity to antigrowth signals, limitless replicative potential, evasion of apoptosis, sustained angiogenesis, and tissue invasion and metastasis. This past decade marked the consolidation of an era in cancer therapy from DNA/mitosis-based mechanisms to strategies manipulating the deregulated molecular pathways that characterize the malignant phenotype (6). Following the rapid advances in molecular-targeted therapy field, several other mechanisms have been elucidated and agents developed since then: DNA epigenetic modulation, heat shock proteins, DNA methylation, and proteasome-ubiquitin are examples of those.

TABLE 3.1
Selected mechanisms and targeted agents studied in R/M SCCHN

1. Cellular Signal Transduction Pathways
1.1 Inhibition of the receptor function
a) Epidermal Growth Factor Receptor <i>cetuximab, panitumumab, zalutumumab, nimotuzumab, trastuzumab, gefitinib, erlotinib, lapatinib,</i>
b) Insulin Growth Factor Receptor Pathway: <i>IMC-A12</i>
c) Hepatocyte Growth Factor and the c-Met Pathway: <i>PF-02341066</i>
1.2 Inhibition of Cytoplasmatic Signal Transduction
a) Ras/Raf/MEK/ERK Pathway Multikinase Inhibitors: <i>sorafenib, sunitinib</i>
b) PI3-K/AKT/mTOR pathway AKT inhibitors: <i>perifosine</i> Mammalian target of rapamycin inhibitors: <i>rapamycin, temsirolimus, everolimus, deforolimus</i> Protein-Kinase C Inhibitors: <i>midostaurin, enzaustarin</i>
c) Farnesyltransferase Inhibitors: <i>lonafarnib</i>
d) Src Family Kinases: <i>dasatinib, AZD-0530</i>
2. Tumor Vasculature <i>bevacizumab, semaxinib, vandetanib, cediranib</i>
3. Cell Cycle Inhibitors
a) Aurora Kinases: <i>MLN8237</i>
b) Cyclin-dependent kinase inhibitors: <i>flavopiridol, seliciclib, UCN-01</i>
4. Other Agents with Transversal Mechanisms
a) The Ubiquitin—Proteasome Pathway: <i>bortezomib</i>
b) Heat Shock Protein: <i>17-AAG, CNF2024</i>
c) Histone Deacetylase Inhibitors: <i>vorinostat, panobinostat</i>
d) Cyclooxygenase-2 Inhibitors
e) PARP-inhibitors

Each of these pathways can be targeted at the molecular level through the use of novel biological agents. A description of the several pathways, classes of drugs, and molecularly targeted agents is shown in Table 3.1 and individually described in this chapter along with their potential role in SCCHN. Noteworthy is that didactically, although these agents have been attributed to a class or a main mechanism of action, because there exist complex, longitudinal nonlinear interactions, and multiple redundant feedback loops occurring among the key targets in signaling pathways, targeted agents commonly affect multiple aspects of cancer biology simultaneously (6).

■ CELLULAR SIGNAL
TRANSDUCTION PATHWAYS

Inhibition of the Receptor Function

Epidermal Growth Factor Receptor (EGFR)

The epidermal growth factor receptor (EGFR) is a member of the erbB family of receptors. The EGFR family of receptor tyrosine kinases is composed of EGFR (HER-1 or erbB-1), HER-2/neu (erbB-2), HER-3 (erbB-3), and HER-4 (erbB-4). All except HER-3 contain an intracellular tyrosine kinase domain and all except HER-2, bind to extracellular ligands. The EGFR family plays an essential

role in normal organ development by mediating morphogenesis and differentiation through effects on cell proliferation, differentiation, apoptosis, invasion, and angiogenesis (7,8).

EGFR expression was first described in SCCHN cell lines in the early 1980s. Overexpression of EGFR occurs in variety of solid tumors and in almost approximately 90% of SCCHN (9–11). Compared to normal mucosa of patients without cancer, SCCHN tumors overexpress EGFR and its ligand, transforming growth factor alpha (TGF- α). In SCCHN tumors, there is a 70- and 5-fold increase in EGFR and TGF- α mRNA, respectively (12). EGFR expression is moderately increased in normal epithelium adjacent to tumor tissue (12), and markedly enhanced when cells transition from dysplasia (13) to carcinoma, supporting the theory of field cancerization and demonstrating that EGFR upregulation is an early event in SCCHN oncogenesis.

In general, most studies have shown that patients with EGFR overexpression have a higher stage, increased lymph node metastasis, shorter relapse-free survival, and overall survival (9–12,14–16). However, other studies have found no correlation between EGFR overexpression and clinical outcome (17,18).

Upon ligand binding (most often amphiregulin and TGF- α in head and neck cancer), EGFR forms a homodimer or heterodimer with other members of the family, resulting in autophosphorylation and activation of downstream signaling cascades. Based on their affinities for their receptors, these ligands are divided into different groups. Epidermal growth factor (EGF), TGF- α , and amphiregulin bind to EGFR; betacellulin, heparin-binding growth factors, and epiregulin can interact with both EGFR and erbB4; and finally, tomoregulins and heregulins bind to erbB4 and occasionally to erbB3 (19,20). HER-2 has no known ligand, but it is the preferred heterodimerization partner for EGFR. Following dimerization of the receptors, intracellular signaling pathways are activated.

Two EGFR targeting strategies are currently being investigated in preclinical and clinical

settings: (a) Anti-EGFR antibodies recognize the ligand-binding domain of EGFR and impair receptor activation; (b) EGFR tyrosine kinase inhibitors bind to the cytoplasmic region of EGFR and impair downstream signaling events.

Monoclonal Anti-EGFR Antibodies

Cetuximab, a humanized mouse anti-EGFR immunoglobulin G1 (IgG1) monoclonal antibody, was the first drug approved by the Food and Drug Administration (FDA) for SCCHN in 40 years. It inhibits activation of the receptor tyrosine kinase and induces antibody-dependent cellular cytotoxicity (21). In addition, it has also been shown to inhibit nuclear EGFR transport and suppress the DNA-dependent protein kinase, a DNA repair mechanism (22). Cetuximab also acts as a tumor-specific radiosensitizer and it has been shown to reduce tumor repopulation during fractionated radiotherapy in a xenografted human model of SCCHN (23,24).

The proof of principle trial in the first-line treatment for R/M SCCHN was conducted by Burtness et al in the Eastern Cooperative Oncology Group (E5397) (25). In a placebo-controlled randomized phase III trial of cisplatin (100 mg/m²) with or without cetuximab (400 mg/m²) loading dose on week 1, followed by 250 mg/m² weekly, a total of 123 patients with SCCHN were accrued. The patients had newly diagnosed metastatic disease or locoregional recurrence/persistence after surgery or radiation therapy. A significant improvement in the objective response rate was observed for the cetuximab plus cisplatin patient group, with 22.66% versus 9.3% ($P = .03$). Though the cisplatin-cetuximab group had a longer progression-free survival (4.2 vs. 2.7 months) and median overall survival (9.2 vs. 8.0 months), the differences did not reach statistical significance. The trial, however, was not adequately powered to demonstrate significant differences in survival endpoints.

The phase II trials reported by Baselga (26) and by Herbst (27) tested the addition of cetuximab to cisplatin in patients who were refractory

to platinum-based combination chemotherapy. Baselga et al treated 96 eligible patients with cetuximab followed by platinum chemotherapy at the same dose and schedule at which progressive disease was documented before entry to the study. It was noted an overall response rate of 10%, median time to progression of 85 days and overall survival of 183 days. Herbst et al enrolled 132 patients to receive two 3-week cycles with cisplatin/paclitaxel or cisplatin/FU. Seventy-six patients with stable or progressive disease received a combination therapy with cetuximab (400 mg/m² intravenously on day 1, then 250 mg/m²/weekly) and cisplatin. After protocol amendment, 54 additional patients who had developed progressive disease within 90 days of platinum-based therapy, also received cetuximab with cisplatin. Cetuximab given with cisplatin achieved an objective response in 9 out of 51 patients who were treated for stable disease, 5 out of 25 patients who had progressed after 2 cycles of chemotherapy, and 3 of 54 patients who had progressed beyond 2 cycles up to 90 days. Vermoken et al (28) also investigated cetuximab monotherapy in a follow-up phase II trial enrolling 103 patients with R/M SCCHN who failed to respond to platinum-based therapy. Thirteen partial responses were documented for an overall response rate of 13%. The median time to disease progression was 70 days, and median overall survival was 178 days.

Building on these results, the Erbitux in First-Line Treatment of Recurrent or Metastatic Head and Neck Cancer (EXTREME) study confirmed the benefit of adding cetuximab to chemotherapy as a first-line treatment in the R/M setting (29). In total, 442 patients with R/M SCCHN, who were not candidates to local therapy and had not received systemic therapy in this disease setting, were randomized to treatment with either cetuximab plus platinum-based chemotherapy (cisplatin or carboplatin plus 5-fluorouracil) or platinum-based chemotherapy alone. Patients received cetuximab at a dose of 400 mg/m² followed by 250 mg/m² weekly until progression

or unacceptable toxicity and either carboplatin (AUC, 5; day 1) or cisplatin (100 mg/m² intravenously; day 1) plus 5-FU (1000 mg/m² intravenously; days 1–4) every 3 weeks, for a maximum of 6 cycles, or the same dose and schedules of platinum plus 5-fluorouracil without cetuximab. Crossover of patients after disease progression was not allowed.

The addition of cetuximab to platinum-based chemotherapy with fluorouracil (platinum–fluorouracil) significantly prolonged the median overall survival from 7.4 months in the chemotherapy-alone group to 10.1 months in the group that received chemotherapy plus cetuximab (hazard ratio for death, 0.80; 95% confidence interval, 0.64 to 0.99; $P = .04$). The addition of cetuximab prolonged the median progression-free survival time from 3.3 to 5.6 months (hazard ratio for progression, 0.54; $P < .001$) and increased the response rate from 20% to 36% ($P < .001$).

These substantial clinical benefits were achieved with no decrease in quality of life associated with the addition of cetuximab to chemotherapy. Of 219 patients receiving cetuximab, 9% had grade 3 skin reactions and 3% had grade 3 or 4 infusion-related reactions. There were no cetuximab-related deaths. In a subset analysis, there was a greater benefit for the following subgroups: those under 65 years of age, those with better performance status, and those who received cisplatin (as three quarters of study participants did). The relative worth of cetuximab in later lines of therapy in R/M disease could not be assessed from this study because there was no crossover. This study established cetuximab, cisplatin, and 5-FU as an option, while leaving open the question of whether cetuximab would have an equal benefit with lesser cost or toxicity if used later in the course of the disease. A summary of the activity of cetuximab in R/M SCCHN is shown in Table 3.2.

Other EGFR receptor blockers have also been investigated. Panitumumab is a fully humanized IgG2 monoclonal antibody with high affinity to the extracellular domain of EGFR (30). Because of its structure (fully human antibody), infusion-related

TABLE 3.2

Efficacy results of selected cetuximab trials in R/M SCCHN

Regimen	Phase	Patient Population	Number of Patients	Response Rate (%)	Median OS (Months)	Ref.
Cisplatin/5-FU with cetuximab	III	First line	222	36	10.1	(29)
Cisplatin with cetuximab	III	First line	57	26	9.2	(25)
Cetuximab with docetaxel	II	Platinum failure	84	10	7.0	(203)
Single agent Cetuximab	II	Platinum failure	103	13	5.9	(28)
Cetuximab with paclitaxel	II	First line	42	60	NA	(204)
Cetuximab with cisplatin/ carboplatin	II	Platinum failure	96	10%	5.5	(26)
Cetuximab with cisplatin*	II	Platinum failure	SD—51	18	SD—11.7	(27)
			PD—79	10	PD1—6.1	
					PD2—4.3	

*Patients initially received 2 cycles of cisplatin + paclitaxel or cisplatin + 5-FU. Patients with stable disease (SD) or whose disease progressed (PD) went onto cisplatin + cetuximab. PD2 corresponds to patients who developed PD within 90 days after platinum-based therapy. NA, not available.

reactions are minimal. In a phase I study of 19 treatment-naïve patients with stage III/IV locally advanced head and neck cancer (LAHNC), panitumumab (2.5 mg/kg) was combined with weekly carboplatin, paclitaxel, and intensity-modulated radiotherapy (70 Gy) (31). Thirteen patients had evaluable primary tumors according to RECIST criteria, and 9/13 (69%) had complete responses, while 4/9 (31%) had partial responses. All 19 patients had evaluable cervical adenopathy, and all 19 had partial responses. Two trials, a phase II evaluating docetaxel and cisplatin combination chemotherapy with and without panitumumab as a first-line treatment for patients with R/M SCCHN (NCT00454779) and a randomized phase III of chemotherapy with or without panitumumab (NCT00460265) are in progress.

Zalutumumab, previously known as HuMax-EGFr, is a completely human IgG1 monoclonal

antibody against human EGFR. The first phase I/II study included 28 patients with R/M SCCHN after failure to conventional treatments and showed promising activity (32,33). In the 2 highest dose groups (4 and 8 mg/kg), 7 of 11 patients obtained a partial response or stable disease and 9 patients obtained metabolic response as assessed by fluoro 2-deoxyglucose positron emission tomography. The most frequent adverse events, all reported as nonserious, were rash or acne, occurring in 16 of 28 patients. A phase III trial that included 273 SCCHN patients who were refractory to or intolerant to standard platinum-based chemotherapy has recently finished accruing (NCT00382031).

Nimotuzumab, previously known as h-R3 is a humanized IgG1 monoclonal anti-EGFR antibody has been approved in several countries for the treatment of head and neck tumors (15)

and glioma (16). A phase I/II study with nimotuzumab in combination with radiotherapy in LAHNC has shown good tolerability and interestingly, no skin toxicity (34). Preliminary analysis from a small phase III study of nimotuzumab combined with radiotherapy or chemoradiation in patients with LAHNC suggested antitumor activity, with an objective response rate of 76% for nimotuzumab and radiotherapy in a group of 17 patients (35). The proposed reason for the low skin toxicity of nimotuzumab might lie in its intermediate affinity and the fact that it does not disrupt the basal ligand-independent level of EGFR signaling (36), being less toxic for normal epithelial cells.

Trastuzumab is a monoclonal antibody directed against HER-2 that has been FDA-approved for breast cancer and investigated in several malignancies. Overexpression of HER-2 is seen in about 15% to 20% of SCCHN (37). Trastuzumab also has a partial ability to disrupt the heterodimerization of HER-2 with other HER family members, suggesting that it is able to impair signaling through other HER receptors (38). A phase II study combining trastuzumab with paclitaxel and cisplatin in 61 patients with R/M SCCHN was reported (39). HER-2 expression, as indicated by membrane staining of $\geq 10\%$ of cells by immunohistochemistry, was rare (7%), and HER-2/neu amplification was absent in all patients. Partial responses were reported in 36% of patients and the median time to progression was 4.3 months. Thus, the single inhibition of HER-2 in this population of unselected SCCHN for HER-2 overexpression or gene amplification was not sufficient. Among the head and neck cancers, only salivary duct carcinoma is reported to be responsive to trastuzumab therapy (40,41).

Tyrosine Kinase Inhibitors

Small molecule EGFR-tyrosine kinase inhibitors can block different growth factor receptor tyrosine kinases, including other members of the EGFR family, or the vascular endothelial growth factor

receptor. The most studied agents in SCCHN are erlotinib and gefitinib.

Gefitinib is an anilinoquinazoline reversible EGFR inhibitor that has been shown to be effective as a single agent in SCCHN cell lines and tumor xenografts as well as a radiosensitizer agent. In a phase II trial with 52 patients (42), of whom 85% had received prior chemotherapy, the overall response rate with gefitinib 500 mg daily was 10.6% and the disease control rate was 53%. Median time to progression and survival were 3.4 and 8.1 months, respectively. The only grade 3 toxicity was diarrhea. A further phase II trial demonstrated similar results, with clinical response in 8% (43) and 15% (44). A dose-response relationship was suggested when a phase II trial with 70 patients showed a response rate of only 1.4% when gefitinib 250 mg daily was used in R/M SCCHN (45). More recently, a randomized, phase III trial of gefitinib versus standard methotrexate including 486 patients who had R/M SCCHN has been reported (46). Patients were stratified based on whether they had received prior platinum-based chemotherapy (group A) or were too ill to receive such treatment (group B). Patients in each group were randomized to 3 treatment arms: oral gefitinib (250 mg or 500 mg daily) or intravenous methotrexate (40 mg/m² weekly with dose escalation to 60 mg/m² weekly) until disease progression. Gefitinib was associated with skin rash in 29% to 39% of patients and with diarrhea in 26% to 39% of patients. Patients who received gefitinib experienced higher rates of tumor-related hemorrhage than those who received methotrexate. Median overall survival was similar in the 3 treatment groups: 5.6, 6.0, and 6.7 months in the gefitinib (250 mg and 500 mg) and methotrexate arms, respectively. However, in patients who received prior platinum-based chemotherapy, those who received methotrexate achieved a better overall survival compared with those who received either 250 mg of gefitinib (hazard ratio, 1.62; $P = .01$) or 500 mg of gefitinib (HR, 1.5; $P = .02$). In group B, no differences in survival were noted among

treatment arms. The overall response rates were 2.7%, 7.6%, and 3.9% in the gefitinib (250 mg and 500 mg) and methotrexate arms, respectively.

The use of gefitinib in combination with conventional chemotherapy in the R/M setting has also been studied. A phase III, randomized trial of docetaxel plus placebo or docetaxel plus gefitinib 250 mg taken orally until disease progression was recently reported (47). The median overall survival was 6.2 months for those who received docetaxel versus 6.8 months for those who received gefitinib in addition. The median time to progression was 2.07 months for single agent docetaxel in contrast with 3.55 months for docetaxel and gefitinib. Although there was a statistically significant difference in time to progression in the patients who received gefitinib, it was not translated into an increased overall survival.

Erlotinib is an orally available, potent, reversible, and selective inhibitor of the EGFR tyrosine kinase. In a large phase II trial including 150 patients (48), an overall response rate to erlotinib 150 mg of 4.3% (95% CI, 1.4%–9.9%) was noted. Lower than that achievable with conventional cytotoxic chemotherapy, it indicated that erlotinib as a single agent was marginally cytoreductive in this patient population. This same trial showed a median duration of disease stabilization of 16.1 weeks in 38% of patients. A further phase I/II trial suggested the recommended phase II dose or erlotinib in combination with cisplatin as being 100 mg daily and cisplatin 75 mg/m² every 21 days (49). This regimen showed a response rate of 21%, with 1 complete response, 8 partial responses, and disease stabilization in 21 patients (49%; 95% CI, 33%–65%). Median progression-free survival was 3.3 (95% CI, 2.7–4.8 months) and median overall survival was 7.9 (95% CI, 5.6–9.5) months. These findings were similar to other phase II of EGFR inhibitors with or without platinum, and it compares favorably to standard cytotoxic platinum-based doublets with respect to its toxicity profile.

Lapatinib is a selective and potent dual, competitive reversible inhibitor of EGFR and HER-2.

In a phase II trial in R/M SCCHN (50), oral lapatinib 1500 mg daily was given to 2 groups of patients, those with and without previous exposure to an EGFR inhibitor. In the 42 evaluable patients, no objective responses were observed in either cohort. In an intent-to-treat analysis, stable disease was observed in 37% of patients in those without prior exposure, and 20% in those who had previously received an EGFR inhibitor. Lapatinib appeared to have little clinical activity as a single agent in patients with SCCHN who were EGFR inhibitor naive or who had refractory disease.

Insulin Growth Factor Receptor Pathway

The insulin-like growth factor system is composed mainly of the circulating ligands, insulin-like growth factor-I (IGF-I), IGF-II, insulin, multiple receptors, and their binding proteins. The type one insulin-like growth factor receptor (IGF-1R) is a tyrosine kinase receptor with a 70% homology to the insulin receptor (51). In normal physiology, ligand activation of IGF-1R plays a role in fetal development and linear growth of the skeleton and other organs. Both preclinical and clinical investigations have implicated the IGF-1R and its ligands in the development and progression of human epithelial tumors (52). Upon ligand binding, downstream activation of signaling cascades that include PI3K/Akt/mTOR and MAPK pathways occur. It has been shown that IGF-1R expression is increased in SCCHN (53,54) and that IGF-1R signaling significantly influences the proliferation, motility, and tumorigenicity of human head and neck cancer cell lines (53). Moreover, IGF-1R expression is inversely related to susceptibility to apoptosis (55).

Morgillo et al showed that erlotinib and gefitinib induce heterodimerization of EGFR/IGF-1R, resulting in the activation of IGF-1R and induction of Akt/mTOR-mediated synthesis of surviving protein (56,57). This interaction would protect non-small lung cancer cells from drug-induced apoptosis and suggests that

targeting both IGF-1R and EGFR may be an effective approach. A phase II clinical trial of the IGF-1R monoclonal antibody IMC-A12 with or without cetuximab in R/M SCCHN is currently in progress (NCT00617734).

Hepatocyte Growth Factor and the C-Met (HGF/Met) Pathway

The receptor tyrosine kinase c-Met and its only known ligand, hepatocyte growth factor/scatter factor (HGF), have become important targets for new therapies. c-Met and HGF have vital roles during normal development, organogenesis, and homeostasis, and their expression is normally confined to cells of epithelial and mesenchymal origin, respectively (58,59). Upon HGF binding, c-Met autophosphorylates and activates downstream several pathways including RAS-RAF-ERK, phosphatidylinositol 3-kinase-AKT-mTOR, and the signal transducer and activator of transcription (STAT) 3 pathway (60–62). The biological effects of HGF/Met have been shown to be important in epithelial–mesenchymal interaction and regulation of cell migration, invasion, cell proliferation and survival, angiogenesis, and morphogenic differentiation (63,64).

Furthermore, Met is overexpressed in a number of solid tumors, and expression correlates with an aggressive phenotype and poor prognosis (63–65). Met overexpression and mutations have been implicated in more invasive SCCHN (66–70) as well as in the metastatic spread (71,72).

Small molecule tyrosine kinase inhibitors as well as antagonistic antibodies to either HGF or c-Met are currently being evaluated in phase I and/or phase II clinical trials for patients with advanced cancers, including SCCHN (73–75). PF-02341066 is an orally available selective Met competitor that has been shown to inhibit tumor cell growth in vitro and in vivo (74,76). Recently, it has been reported by Seiwert et al (77) that Met inhibition by PF-02341066 in SCCHN tumors disrupted Met signaling, cell viability, motility/migration in vitro, and tumor angiogenesis in vivo. Inhibition of cell growth was also observed

when combining a Met inhibitor with cisplatin or erlotinib. Other agents under development include GSK1363089/XL880, XL184 (Exelixis), ARQ 197 (ArQule Inc.), SGX523 (SGX Pharmaceuticals), and MGCD265 (MethylGene).

Inhibition of Cytoplasmatic Signal Transduction

Ras/Raf/MEK/ERK Pathway

The Ras-Raf-MEK-ERK pathway represents a common downstream pathway for several key growth factor tyrosine kinase receptors, which are often mutated or overexpressed in human cancers. Notably, this pathway is part of the downstream signaling cascades of both EGFR and the Met receptor tyrosine kinases (78,79). Although mutations in *ras* or *BRAF* genes are rare with only approximately 3.5% of patients with LAHNC presenting K-RAS codon 12 mutations (80), members of the *ras* family are overexpressed in SCCHN, (81–85) and in vitro evidence suggests that the level of K-ras expression is a determinant of proliferation of SCCHN cell lines (81). Thus, the EGFR-Ras-Raf-MEK-ERK signaling pathway in SCCHN is an attractive therapeutic target.

Multikinase Inhibitors

Sorafenib is a multiple tyrosine kinase inhibitor, targeting vascular endothelial cell growth factor receptor (VEGFR-2 and 3), platelet-derived growth factor receptor (PDGFR)- β , c-Kit, and rearranged during transfection (RET), as well as inhibiting downstream Raf kinase isoforms (wild-type Raf-1, B-Raf, and mutant *b-raf* V600E) (86). By targeting the EGFR-Ras-Raf-MEK-ERK signaling pathway as well as tumor angiogenesis, this agent has been the most studied multikinase inhibitor in SCCHN. A phase II Southwest Oncology Group trial assessed sorafenib as a single agent in 44 chemotherapy naive patients with R/M SCCHN (87). With an overall

survival of 8 months (95% CI, 7–11 months), sorafenib was well tolerated, one patient had a partial response (3%) and 14 patients (45%) had stable disease. The response rate was 3% (95% CI, 0%–13%). A further phase II trial evaluated single agent sorafenib in 27 patients with R/M SCCHN (20) or nasopharyngeal carcinoma (7) (88). With an overall survival of 4 months, 1 patient had a partial response (4%), and 10 patients (37%) had stable disease.

Two phase II studies of sunitinib in R/M SCCHN patients were disappointing. A study performed at the University of Chicago was closed after an interim analysis of 19 patients, with only one partial response (89). Another recent study revealed no objective response of sunitinib in 17 patients R/M SCCHN (90). Most recently, 38 patients with SCCHN having evidence of progressive disease were treated with sunitinib 37.5 mg/day given continuously until progression or unacceptable toxicity. A partial response was observed in only one patient and stable disease in 18 (91). A major issue in development of multi-kinase inhibitors is the surge of mutant inhibitor kinases, thus the interest in the combination with conventional chemotherapy and/or with other targeted therapies in an attempt to optimize efficacy.

PI3-K/Akt/mTOR Pathway

Since activation of Akt is a frequent event in SCCHN (92), inhibitors that target the PI3/Akt/mTOR pathway have been extensively investigated.

The phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) pathway regulates numerous cellular processes such as growth, proliferation, cell cycle progression, motility, adhesion, and angiogenesis. The phosphatidylinositol 3-kinase/protein kinase B/serine-threonine kinase mammalian target of rapamycin-pathway has been implicated in all major mechanisms of radioresistance (93) and in the development and progression of SCCHN by promoting cellular survival and resistance to

apoptosis (94). This pathway has been shown to be activated in up to 50% to 80% of SCCHN (95). It has also been proposed that Akt activation, PI3K accumulation, and phosphatase and tensin homolog downregulation detected in SCCHN could reflect the early biochemical effects of tobacco components such as nicotine (96,97). Moreover, Akt activation has also been correlated with adverse outcomes in tongue cancer (98).

AKT Inhibitors

A phase II trial involving the nonspecific Akt phosphorylation/activation inhibitor perifosine in a small group of patients with incurable, R/M SCCHN showed no objective clinical responses with 18 of 19 patients having disease that progressed at 8 weeks (99). Akt activation, however, has also been associated with resistance to EGFR inhibition in a non-small cell lung cancer model (100), and the combination of novel better AKT inhibitors with anti-EGFR agents is an attractive venue of investigation.

Mammalian Target of Rapamycin

(mTOR) Inhibitors

Another critical pathway by which Akt promotes cell growth and survival is by the activation of mTOR. Once activated, mTOR executes its biological functions through 2 distinct complexes, mTORC1 and mTORC2. The mTORC1 complex consists of mTOR, mLST8, and raptor (regulatory-associated protein of mTOR). The mTORC2 complex consists of mTOR, mLST8, mSIN1 (mitogen-activated protein kinase-associated protein (1), and rictor (rapamycin insensitive companion of mTOR), which have differential sensitivities to rapamycin. Rapamycin is currently believed to be a cell-type-dependent inhibitor of mTORC2 function as well as a universal inhibitor of the mTORC1 pathway (101). mTORC2 is responsible to regulate cell polarity and spatial growth (102). TORC1 acts through its downstream effectors to facilitate cell cycle progression from G1 into S phase by

phosphorylating 2 important cell constituents, p70S6 kinase (p70S6K) and 4E-binding protein 1 (4E-BP1). Through phosphorylation of the eukaryotic initiation 4E-BP1, mTOR permits formation of the eIF-4F complex that promotes cap-dependent protein translation (103). The primary substrate of p70S6K, the ribosomal protein S6 kinase 1, has been shown to have an important role in determining cell size (104,105).

Rapamycin is a macrolide antibiotic derived from the bacteria *Streptococcus hygroscopicus*. Although FDA-approved as an immunosuppressant, it has not been widely tested in malignancies. The rapamycin analogues temsirolimus (CCI-779), everolimus (RAD-001), and deforolimus (AP-23573) have then been developed as cancer drugs. Temsirolimus is an ester of rapamycin that is available as an intravenous or oral formulation. It was granted FDA approval for poor-risk untreated advanced renal cell carcinoma patients. The most common grade 3 and 4 toxicities are asthenia, anemia, and dyspnea. Everolimus is an oral mTOR inhibitor that is approved in Europe as an immunosuppressive agent for solid organ transplantation. A third mTOR inhibitor, deforolimus, can be delivered orally or intravenously and the dose-limiting toxicity found in a recent published phase I trial in advanced malignancies, that included one patient with SCCHN, was mouth sores (106). In another phase I study with deforolimus and capecitabine, 1 patient with advanced SCCHN was reported to have stable disease for approximately 4 months (107).

In a recent report (108), 2 squamous cell carcinoma cell lines, 1 resistant and 1 of intermediate susceptibility to EGFR inhibitors were xenografted in vivo and treated with temsirolimus, erlotinib, or a combination of both. Temsirolimus exerted superior growth arrest in both cell lines than erlotinib and marked anti-tumor effects were associated with dual pathway inhibition.

However, rapamycin-induced Akt activation has also been observed in some cancer cell lines and in clinical trials. This effect is attributed

to S6K1, which when stimulated by activated mTOR, phosphorylates insulin receptor substrate proteins, inhibiting their function, which in turn diminishes signaling through the PI3K/AKT pathway (109–111). And by inhibiting the natural negative feedback on IGF-1R, mTOR inhibition can also potentially increase PI3-K and Akt activation and counteract the initial inhibitory effects on the pathway. This loop could be potentially disrupted by using mTOR inhibitors in combination with antagonists of upstream signaling, such as IGF-1R inhibitors (112). Furthermore, phase II and III trials evaluating the combination of mTOR inhibitors with EGFR and IGF-1R inhibitors are in progress in several solid tumors, including SCCHN.

Protein-Kinase C (PKC) Inhibitors

PKC belongs to a family of serine/threonine kinases that regulate a variety of cell functions including cell growth, cell cycle progression, differentiation, cytoskeleton organization, cell migration, tumor angiogenesis, and apoptosis (113). The PKC isoforms, and in particular the PKC ζ isoform, were shown in vivo to be valid targets in SCCHN based on their high expression pattern in malignant disease, their critical role in EGFR-dependent mitogen-activated protein kinase activation, and their ability to inhibit SCCHN proliferation (114). Midostaurin and enzaustarin are the kinase inhibitors currently under investigation.

Farnesyltransferase Inhibitors

The farnesyltransferase inhibitors were designed to inhibit the posttranslational processing of Ras proteins (115). In preclinical models, farnesyltransferase inhibitors showed great potency against SCCHN cells (116). A phase II trial of lonafarnib, an agent that specifically inhibits farnesyl protein transferase, in 15 patients with cisplatin-refractory R/M SCCHN (117) demonstrated no objective response. However, as preclinical data have suggested that blockade of farnesyltransferase may potentiate EGFR inhibition in SCCHN cells (116),

there are also compelling arguments for the combined use of these agents with EGFR inhibitors in further studies.

Src Family Kinases

Src kinases have been implicated in normal cellular functions including cell adhesion, migration, angiogenesis, survival, proliferation, and differentiation (118). Src is the prototype member of a family of nonreceptor cytoplasmatic tyrosine kinases that function as transducers of mitogenic signaling downstream to a number of receptor tyrosine kinases including fibroblast growth factor receptor (FGFR), platelet derived growth factor (PDGFR), colony-stimulating factor-1 receptor (CSF-1R), and EGFR (119). Src kinases have been shown to potentiate EGFR signaling in several malignancies (120,121). In SCCHN, Src kinases are activated in response to EGFR stimulation (122) and have reduced activity following EGFR inhibition *in vitro* (123).

Dasatinib (BMS-354825) is an ATP-competitive tyrosine kinase inhibitor that sensitively inhibits all members of the Src family and at higher concentrations is capable of inhibiting the Src kinases ABL, c-Kit, PDGFR, and EphA2 (124). Because of its ability to inhibit BCR-ABL, dasatinib was developed and approved by the FDA for chronic myeloid leukemia and acute lymphoblastic leukemia. However, the only phase II trial in R/M SCCHN reported did not show any response (125). In 13 evaluable patients for response and 15 for toxicities, overall response rate was 0 and toxicity led to hospitalization in 4 and drug discontinuation in 5 patients. AZD-0530 is a more selective c-Src and BCR-ABL inhibitor that has also been investigated. A phase II trial in R/M SCCHN is in progress (NCT00513435).

■ TUMOR VASCULATURE

Angiogenesis is the process of neovascularization to support growth in both normal and tumor

tissues. Among the proangiogenic factors, the vascular endothelial growth factor (VEGF) plays a central role in new vessel formation. Several cytokines are produced in SCCHN that induce angiogenesis (126,127). VEGF expression is regulated by hypoxia-inducible factor-1 α (HIF-1 α) dependent and independent mechanisms involving PI3-K and AKT. HIF-1 α levels rise rapidly under hypoxic conditions and induce the transcription of multiple genes including VEGF, endothelin-1, and c-Met (128). The high levels of VEGF observed in EGFR-inhibitor resistant tumors as well as the upregulation of VEGF levels by EGFR activation are the rationale for using molecular therapies that target both EGFR and VEGF (129,130). Several ongoing trials are testing the potential of angiogenesis inhibitors in SCCHN combined with chemotherapy and other targeted agents.

Notably, single-agent antiangiogenic drugs have not been effective in unselected SCCHN patients with a greater activity when combined with other agents. Given the initially proposed mechanism of inhibiting neovascularization and regression of tumor vasculature, the opposite would be expected. However, the consequent reduced vascular permeability and intratumor pressure also lead to an increase in delivery of oxygen and therapeutic agents to tumors (131).

The humanized recombinant monoclonal antibody to the VEGF bevacizumab has been the most studied antiangiogenic agent. A phase II study of bevacizumab and erlotinib in R/M SCCHN has recently been reported (132). In the 48 patients assessed, the best observed response included complete or partial response in 7 patients (15%; 95% CI, 6–28) and stable disease in 15 patients. Four patients had a complete response. The median overall survival was 7.1 months (95% CI, 57–90), with 15 patients surviving 1 year, and the median progression-free survival time was 4.1 months (2.8–4.4). The most common toxic effects of any grade were rash and diarrhea (41 and 16 of 48 patients, respectively). Three patients had serious bleeding events of grade 3 or higher,

one of which was fatal, ascertained at autopsy to be laryngeal in origin, but not at a site of active disease. Another trial evaluating bevacizumab and cetuximab revealed a partial response in 5 (20%) and stable disease in 14 (56%) of 25 evaluable patients (133,134). In these 2 studies, patients were allowed up to one prior regimen for their R/M disease. When bevacizumab was combined with the antifolate pemetrexed in previously untreated R/M disease in a phase II trial, an interim analysis showed an overall response of 36% (135). In 22 evaluable patients, 3 (14%) had complete response, 5 had (23%) partial response, and 13 (59%) had stable disease. Two deaths were reported, one from sepsis in a neutropenic febrile patient and another from tracheal bleeding in a previously reirradiated area triggered by suctioning. Three hemorrhagic events were reported.

Other small molecule kinase inhibitors targeting angiogenesis have also been investigated. Semaxinib (SU5416), a synthetic small molecule inhibitor of the tyrosine kinase domain of vascular endothelial growth factor receptor 2 (VEGFR2), was evaluated in a phase II trial of 32 treatment refractory patients with SCCHN (136). Of 31 patients available for response assessment, there was 1 partial response and 1 minor response, with median overall survival of 6.25 months.

Vandetanib (ZD6474) has shown potent, selective activity against VEGF receptor-2 and has activity against EGFR, and RET tyrosine kinases. VEGFR-2 is considered to be the dominant signaling receptor for endothelial cell permeability, proliferation, and differentiation (137) and in vivo ZD6474 was a highly active antitumor agent for SCCHN by induction of tumor cell apoptosis and inhibition of VEGF-dependent angiogenesis (138). The dual activity of vandetanib allows a single molecularly targeted agent to inhibit 2 key pathways in tumor growth by targeting the tumor vasculature and the tumor cell population.

Another promising agent is cediranib (AZD2171), an oral, highly potent, and selective inhibitor of VEGF signaling, with activity versus VEGFR-1, -2, and -3. It has recently been

shown to have evidence of antitumor activity in an open label exploratory study that included 15 patients with R/M SCCHN, (139) with 3 partial responses by the response evaluation criteria in solid tumors. It is currently being tested as monotherapy in this setting in a single-arm phase II trial (NCT00458978). Selected trials from antiangiogenic and multikinase inhibitors in R/M SCCHN are shown in Table 3.3.

■ CELL CYCLE INHIBITORS

The cell cycle includes several precisely coordinated events and checkpoints that include the postmitotic G1 phase, DNA synthesis S phase, G2 phase, and mitotic M phase. Most chemotherapeutic agents exert their function by acting at different phases of the cell cycle. Specific proteins related to the cell cycle are potential targets of a new generation of drugs.

Aurora Kinases

The aurora kinases belong to a family of cell cycle-regulating serine-threonine kinases and consists of 3 members called A, B, and C. Deregulation of aurora kinase activity can result in mitotic abnormality and genetic instability, leading to defects in centrosome function, spindle assembly, chromosome alignment, cytokinesis, and eventually cell death (140). Aurora A localizes to centrosomes from the late S phase to mitosis and primarily regulates centrosome maturation and separation and consequently controls spindle assembly and stability. Aurora B is part of the chromosomal passenger protein complex, localizing to centrosomes and mitotic spindles during different phases of mitosis (141). It has been shown that Aurora Kinase A messenger RNA overexpression is strongly correlated with tumor progression, a metastatic phenotype, and shortened disease-free survival and overall survival in SCCHN, (142) and Aurora-B expression level was significantly higher in oral squamous cell carcinoma than in normal epithelium (143).

TABLE 3.3

Antiangiogenic agents and multikinase inhibitors in R/M SCCHN

Agent	Phase	Regimen	Patient Population	Number of Patients	Response Rate (%)	Ref.
Bevacizumab	II	+ Cetuximab	First or second line	25	20	(133,134)
	II	+ Pemetrexed	First line	25	36	(135)
	II	+ Erlotinib	First or second line	51	15	(132)
Cediranib	II	Single agent	First or second line	15	20	(139)
Semaxinib	II	Single agent	First to third line	31	6	(136)
Sorafenib	II	Single agent	First line	44	3	(87)
	II	Single agent	Second line SCCHN and NPC	27	4	(88)
Sunitinib	II	Single agent	First to third line	19	5	(89)
	II	Single agent	First line	17	0	(90)
	II	Single agent	First or second line	38	2	(91)

Several small molecule Aurora kinase inhibitors are undergoing preclinical or early clinical development. Preliminary clinical data from phase I trials have largely been consistent with cytostatic effects, with disease stabilization as the best response achieved in solid tumors. Objective responses have been noted in leukemia patients, although this might conceivably be due to inhibition of the ABL kinase (144,145). A phase I/II trial of the Aurora kinase A inhibitor MLN8237 is currently recruiting patients with SCCHN (NCT01045421).

Cyclin-Dependent Kinases (CDK) Inhibitors

The cell division cycle is regulated by the fluctuating activity of cyclin-dependent kinase (CDK)/cyclin pairs (146). Cyclin-dependent kinase inhibitors in clinical development include flavopiridol, seliciclib, UNC-01, and BMS-387032.

Flavopiridol, an intravenous cdk inhibitor is the most potent known inhibitor of cdk9 and has shown to have antitumor activity in both SCCHN cell and xenografts models (147). In phase I solid tumor studies, the dose-limiting toxicity of flavopiridol was neutropenia with bolus schedules (148) and

diarrhea on continuous infusion schedules (149). A phase II trial in R/M SCCHN has finished accrual (NCT00020189) and results are awaited.

Seliciclib is a cdk9, cdk7, and cdk2 orally bioavailable inhibitor that has demonstrated antiproliferative activity in SCCHN cells (150) and a recent phase II trial reported prolonged stable disease in patients with previously treated nasopharyngeal carcinoma (151). Another interesting cdk inhibitor under development is 7-Hydroxystaurosporine (UCN-01), which has also been shown to have activity in SCCHN cells (152). In addition to inhibiting CDKs 2, 4, 6, it also inhibits the protein kinase C and the Akt signaling through PDK1 inhibition (153).

■ OTHER MECHANISMS

The Ubiquitin—Proteasome Pathway

All the eukaryotic cells have a precise control between protein degradation and de novo synthesis. Lysosomal and proteasomal degradation are the 2 major pathways for cellular protein turnover

with the ubiquitin—proteasome pathway being responsible for 80% of cellular protein degradation. Protein substrates are tagged with a poly-ubiquitin chain and then degraded to peptides and free ubiquitin (154). The destruction of regulatory proteins is irreversible and involved in the physiological regulation of signal transduction, transcription, cell cycle, and antigen processing. Preclinical studies have shown that protease blockage inhibits proliferation, induces apoptosis, and sensitizes malignant cells to the proapoptotic effects of conventional chemotherapy and radiation (155).

Among the proteins that are regulated by the proteasome is the inhibitor of nuclear factor- κ B (I κ B). The accumulation of I κ B on proteasome inhibition is responsible for the downregulation of the antiapoptotic NF- κ B (156). Constitutive activation of NF- κ B and activator protein-1 (AP-1) signal transduction pathways have been identified as prominent events promoting tumor progression of hematologic and solid malignancies, including SCCHN (157–159). Ultimately, targeting the proteasome inhibits the nuclear translocation of the NF- κ B that would be triggered by chemotherapy and radiation (154,160). In addition, the antitumor effects of the proteasome inhibitors involve other mechanisms including cell cycle inhibition through increased p53-mediated apoptosis (161), p21- and p27-mediated induction of cell cycle arrest, inhibition of Bcl-2 by Bax (162), and downregulation of p44/42-dependent cell proliferation and survival signals (163).

Bortezomib (Velcade/PS-341), a boronic acid derivative is a reversible 26S proteasome inhibitor that has recently been FDA-approved for the treatment of multiple myeloma and mantle cell lymphoma. Its common toxicities include peripheral sensory neuropathy and gastrointestinal symptoms. A recent phase I trial which included 12 patients with R/M SCCHN showed that the combination of bortezomib, weekly cisplatin, and radiotherapy in SCCHN is feasible and active (164). Phase II trials are currently in progress, including the combination with irinotecan (NCT00103259), gemcitabine (NCT00305734), and docetaxel (NCT00425750).

Heat Shock Protein: The Cancer Chaperone

Heat shock protein 90 (HSP90) is a molecular chaperone that promotes posttranslational folding and stabilization of ‘client’ proteins and protects them from degradation and environmental stress, including hypoxia, heat, radiation, and chemotherapy (165). They are among the most abundant proteins in the cytosol of eukaryotic cells, accounting for 1% to 2% of all proteins (166). Many of its known clients are protein kinases or transcription factors involved in multiple signal transduction pathways, including BCR-ABL, EGFR, RAF, BRAF, AKT, Met, IGF-1R, VEGFR, FLT3, androgen and estrogen receptors, hypoxia-inducible factor (HIF)-1 α , and telomerase (167). In the event of client proteins not being chaperoned by the mature HSP90 complex, they are degraded by the ubiquitin proteasome pathway (168).

Furthermore, HSP90 is constitutively expressed at 2- to 10-fold higher levels in tumor cells compared with normal cells (169,170) and its inhibition leads to degradation of the client proteins and enhances tumor cell death in a variety of cell lines and tumor models, including SCCHN (169,171,172).

17-(Allylamino)-17-demethoxygeldanamycin (17-AAG) was the first HSP90 inhibitor to enter clinical trials. Preclinical studies have shown that 17-AAG can enhance tumor cell sensitivity to radiation (172) and has activity in SCCHN cell lines (173). However, in addition to the lack of objective response in phase I trials (174), 17-AAG has a poor solubility and troublesome formulation (175). Second and third generations HSP90 inhibitors are under development and some, such as CNF2024 (BIIB021) (169,176), may be particularly useful in SCCHN. This agent has been recently shown to enhance the in vitro radiosensitivity of SCCHN cell lines and to have an improved antitumor effect in xenograft studies when compared to 17-AAG.

Histone Deacetylase (HDAC)

Inhibitors—Epigenetic Modulators

Epigenetics refers to the alternate phenotypic states that are heritable changes in gene expression that are not coded in the DNA sequence itself,

and are potentially reversible, but are generally maintained stable during cell division (177,178). Epigenetic changes include modifications of DNA and posttranslational modifications in its associated proteins, most notably the core nucleosomal histones. The process of histone deacetylation is a well-known epigenetic modification and promising therapeutic target (179).

Histone proteins organize DNA into nucleosomes, which are regular repeating structures of chromatin. The acetylation status of histones alters chromatin structure, which, in turn, is involved in gene expression (180,181). Histone acetylation is regulated by 2 enzyme families: HDACs and histone acetyltransferases. These enzymes regulate the acetylation of histone proteins as well as nonhistone proteins, including transcription factors involved in cell cycle progression and apoptosis, such as HSP90, Raf, Akt, erb2, and BCR-ABL (182).

Altered expression and/or genetic defects of HDAC and histone acetyltransferases have been identified in numerous cancers, including SCCHN (183). However, at clinically achievable concentrations HDAC inhibitors have not been shown to be cytotoxic as single agents. Thus, from the onset of their development as oncology drugs, it has been commonly assumed that they would ultimately be used in combination (184). Interestingly, HDAC inhibitors enhance NF- κ B activation in SCCHN, resulting in HDAC inhibitor resistance in vitro, which can be reversed with the combination with bortezomib (185).

Vorinostat (Suberoylanilide hydroxamic acid) is FDA-approved HDAC inhibitor for cutaneous T-cell lymphoma. It has also been shown to have growth inhibitory and apoptosis-inducing effects in SCCHN cells in vitro (186). Several phase I clinical trials of vorinostat in solid and hematological tumors have been completed. In a phase I trial including 4 chemotherapy-naïve patients with R/M SCCHN, the combination of vorinostat, carboplatin, and paclitaxel, resulted in one partial and 2 stable disease as best responses (187).

Vorinostat has also been tested in a phase II trial in 12 heavily pretreated patients with R/M SCCHN (188). Three patients had stable disease ranging from 9 to 26 weeks and no partial or complete responses were noted. Grades 3–4 drug-related toxicities included thrombocytopenia ($n = 3$), anorexia ($n = 2$), and dehydration ($n = 2$). Overall, vorinostat was generally well tolerated but did not demonstrate efficacy defined by tumor response. Panobinostat (LBH589) is a novel HDAC inhibitor under investigation and a phase I/II trial in combination with erlotinib is currently recruiting patients (NCT00738751).

Cyclooxygenase-2 (COX-2) Inhibitors

COX-2, an enzyme responsible for elevated prostaglandin levels in chronic inflammation and cancer, is expressed in the majority of human epithelial tumors and overexpressed in SCCHN (189). Its overexpression was also correlated with poor prognosis in oral SCCHN. COX-2 is responsible for several downstream events, including suppression of apoptosis, cell proliferation, immune response, and angiogenesis. (190,191) COX-2 inhibitors were shown to prevent tongue carcinomas in a rat tongue carcinogenesis model, (192) growth of SCCHN in a mouse xenograft model, (193) and to have radiosensitizing effects in other tumor models (194,195).

COX-2 inhibitors have been investigated particularly when combined with EGFR inhibitors, due to the interaction between EGFR and COX-2 signaling pathways at several levels that include the PI3K/Akt and ras/MAPK pathways. The combination of celecoxib and gefitinib was tested in a phase I study in 19 patients with unresectable recurrent locoregional and/or distant metastatic SCCHN (196). No dose-limiting toxicities were encountered with the combination of celecoxib 400 mg twice and gefitinib 500 mg once daily, and the most common toxicities were acneiform rash, diarrhea, hand reaction, dyspepsia, and anemia. No complete responses were seen, and 4 of 18 patients (22%; 95% CI, 2%–42%) achieved a confirmed partial response.

Other promising uses of COX-2 inhibitors include chemoprevention (197) and in combination with cytotoxic chemotherapy (198).

Parp-Inhibitors: The Chemo/Radiosensitizers

As previously mentioned, DNA mechanisms are activated to arrest cells at several phases of the cell cycle when DNA damage is detected. The poly (ADP-ribose) polymerases (PARP) act as a cellular sensor for DNA breaks and are involved in the repair of DNA single strand breaks. PARP-1 is the principal isoform involved in the cellular process, (199) whereas PARP-2, and other PARP members constitute the residual activities (10%) when PARP-1 is inhibited. PARPs catalyze the transformation of β -nicotinamide adenine dinucleotide (NAD⁺) into nicotinamide and poly (ADP-ribose) polymers. Once bound to DNA lesions, PARP becomes activated and poly ADP-ribosylates many DNA-binding proteins, allowing DNA-repair proteins to access the DNA breaks.

Consistent with its mechanism of action, the first clinical application of the PARP inhibitors in cancer therapy was in combination with DNA damaging agents (e.g., temozolomide, platinum, topoisomerase inhibitors, and radiation). These cytotoxic agents cause DNA damage and thus, induce PARP-1 activity, allowing tumor cells to withstand stress. As a consequence, inhibition of PARP-1 through small molecules sensitizes tumor cells to DNA damaging agents (200,201).

The use of PARP inhibitors in SCCHN has still been very limited, yet promising. A recent study demonstrated that the inhibition of DNA repair by the PARP inhibitor GPI-15427 induced significant sensitization to radiotherapy in a xenograft mouse model of SCCHN, (202) and we expect this will be an area of increasing interest in the following years.

■ CONCLUSION

Recurrent and metastatic SCCHN is still a devastating disease with a poor prognosis. Nevertheless, in the era of personalized medicine, the better

understanding of the molecular biology of SCCHN and the availability of new technologies represent the long awaited hope for these patients and a major step forward in SCCHN research. After decades without significant progress, cetuximab was the first targeted therapy shown to have benefit when combined to a standard chemotherapy regimen in this setting. The response rate nearly doubled with the use of cetuximab in the EXTREME trial, with tolerable and limited toxicity, which represented an important step in the palliative setting. The standard treatment practice for patients with metastatic SCCHN includes single-agent therapy, platinum doublets, and now triplet regimens.

On the other hand, several challenges lie ahead. The overwhelming number of new compounds will require novel and innovative clinical trial designs to efficiently validate these agents and distinguish the hope from the hype. The optimal first-line regimen, exact sequencing of agents in first-line or second-line therapy, and whether biologics should be used in combination with chemotherapy will still be a topic for years to come. Other end points such as disease stabilization and quality of life should be developed further. The identification of predictive factors and a targeted group of patients most likely to have maximal responses with minimal toxicity is the next milestone. There is now compelling evidence that HPV infection is a favorable independent prognostic factor and future trials should incorporate this factor. At the same time, the costs associated with developing these targeted therapies represent an obstacle to developing the agents in less common malignancies such as SCCHN.

This is just the beginning of a new era in cancer treatment. Several agents and mechanisms described in this chapter are being explored and are in different phases of development. Although much remains to be elucidated, the promising early phase data in preclinical and clinical settings presented in this chapter suggest that ongoing and future clinical trials will translate into major advances in the near future that should further improve the benefits of therapy for patients with SCCHN.

■ REFERENCES

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer Statistics, 2009. *CA Cancer J Clin*. 2009; 59(4):225–249.
2. Colevas AD. Chemotherapy options for patients with metastatic or recurrent squamous cell carcinoma of the head and neck. *J Clin Oncol*. 2006;24(17):2644–2652.
3. Gibson MK, Li Y, Murphy B, et al. Randomized phase III evaluation of cisplatin plus fluorouracil versus cisplatin plus paclitaxel in advanced head and neck cancer (E1395): an intergroup trial of the Eastern Cooperative Oncology Group. *J Clin Oncol*. 2005;23(15):3562–3567.
4. Leon X, Hitt R, Constenla M, et al. A retrospective analysis of the outcome of patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck refractory to a platinum-based chemotherapy. *Clin Oncol (R Coll Radiol)*. 2005;17(6):418–424.
5. Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell*. 2000;100(1):57–70.
6. Dy GK, Adjei AA. Systemic cancer therapy: evolution over the last 60 years. *Cancer*. 2008;113(7) (suppl):1857–1887.
7. Partanen AM. Epidermal growth factor and transforming growth factor- α in the development of epithelial-mesenchymal organs of the mouse. *Curr Top Dev Biol*. 1990;24:31–55.
8. Adamson ED. Developmental activities of the epidermal growth factor receptor. *Curr Top Dev Biol*. 1990;24:1–29.
9. Rubin Grandis J, Melhem MF, Barnes EL, Twardy DJ. Quantitative immunohistochemical analysis of transforming growth factor- α and epidermal growth factor receptor in patients with squamous cell carcinoma of the head and neck. *Cancer*. 1996;78(6):1284–1292.
10. Santini J, Formento JL, Francoual M, et al. Characterization, quantification, and potential clinical value of the epidermal growth factor receptor in head and neck squamous cell carcinomas. *Head Neck*. 1991;13(2):132–139.
11. Dassonville O, Formento JL, Francoual M, et al. Expression of epidermal growth factor receptor and survival in upper aerodigestive tract cancer. *J Clin Oncol*. 1993;11(10):1873–1878.
12. Grandis JR, Twardy DJ. Elevated levels of transforming growth factor α and epidermal growth factor receptor messenger RNA are early markers of carcinogenesis in head and neck cancer. *Cancer Res*. 1993;53(15):3579–3584.
13. Rubin Grandis J, Twardy DJ, Melhem MF. Asynchronous modulation of transforming growth factor α and epidermal growth factor receptor protein expression in progression of premalignant lesions to head and neck squamous cell carcinoma. *Clin Cancer Res*. 1998;4(1):13–20.
14. Xia W, Lau YK, Zhang HZ, et al. Combination of EGFR, HER-2/neu, and HER-3 is a stronger predictor for the outcome of oral squamous cell carcinoma than any individual family members. *Clin Cancer Res*. 1999;5(12):4164–4174.
15. O-charoenrat P, Rhys-Evans PH, Archer DJ, Eccles SA. C-erbB receptors in squamous cell carcinomas of the head and neck: clinical significance and correlation with matrix metalloproteinases and vascular endothelial growth factors. *Oral Oncol*. 2002;38(1):73–80.
16. Storkel S, Reichert T, Reiffen KA, Wagner W. EGFR and PCNA expression in oral squamous cell carcinomas—a valuable tool in estimating the patient's prognosis. *Eur J Cancer B Oral Oncol*. 1993; 29B(4):273–277.
17. Leonard JH, Kearsley JH, Chenevix-Trench G, Hayward NK. Analysis of gene amplification in head-and-neck squamous-cell carcinoma. *Int J Cancer*. 1991; 48(4):511–515.
18. Wen QH, Miwa T, Yoshizaki T, Nagayama I, Furukawa M, Nishijima H. Prognostic value of EGFR and TGF- α in early laryngeal cancer treated with radiotherapy. *Laryngoscope*. 1996;106(7):884–888.
19. Riese DJ, Kim ED, Elenius K, et al. The epidermal growth factor receptor couples transforming growth factor- α , heparin-binding epidermal growth factor-like factor, and amphiregulin to Neu, ErbB-3, and ErbB-4. *J Biol Chem*. 1996;271(33):20047–20052.
20. Riese DJ, Komurasaki T, Plowman GD, Stern DF. Activation of ErbB4 by the bifunctional epidermal growth factor family hormone ephregrin is regulated by ErbB2. *J Biol Chem*. 1998;273(18):11288–11294.
21. Bernier J, Bentzen SM, Vermorken JB. Molecular therapy in head and neck oncology. *Nat Rev Clin Oncol*. 2009;6(5):266–277.
22. Dittmann K, Mayer C, Rodemann HP. Inhibition of radiation-induced EGFR nuclear import by C225 (Cetuximab) suppresses DNA-PK activity. *Radiother Oncol*. 2005;76(2):157–161.
23. Milas L, Mason K, Hunter N, et al. In vivo enhancement of tumor radioresponse by C225 anti-epidermal growth factor receptor antibody. *Clin Cancer Res*. 2000;6(2):701–708.
24. Harari PM, Huang SM. Head and neck cancer as a clinical model for molecular targeting of therapy:

- combining EGFR blockade with radiation. *Int J Radiat Oncol Biol Phys*. 2001;49(2):427–433.
25. Burtneß B, Goldwasser MA, Flood W, Mattar B, Forastiere AA. Phase III randomized trial of cisplatin plus placebo compared with cisplatin plus cetuximab in metastatic/recurrent head and neck cancer: an Eastern Cooperative Oncology Group study. *J Clin Oncol*. 2005;23(34):8646–8654.
 26. Baselga J, Trigo JM, Bourhis J, et al. Phase II multicenter study of the antiepidermal growth factor receptor monoclonal antibody cetuximab in combination with platinum-based chemotherapy in patients with platinum-refractory metastatic and/or recurrent squamous cell carcinoma of the head and neck. *J Clin Oncol*. 2005;23(24):5568–5577.
 27. Herbst RS, Arquette M, Shin DM, et al. Phase II multicenter study of the epidermal growth factor receptor antibody cetuximab and cisplatin for recurrent and refractory squamous cell carcinoma of the head and neck. *J Clin Oncol*. 2005;23(24):5578–5587.
 28. Vermorken JB, Trigo J, Hitt R, et al. Open-label, uncontrolled, multicenter phase ii study to evaluate the efficacy and toxicity of cetuximab as a single agent in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck who failed to respond to platinum-based therapy. *J Clin Oncol*. 2007;25(16):2171–2177.
 29. Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med*. 2008;359(11):1116–1127.
 30. Martinelli E, De Palma R, Orditura M, De Vita F, Ciardiello F. Anti-epidermal growth factor receptor monoclonal antibodies in cancer therapy. *Clin Exp Immunol*. 2009;158(1):1–9.
 31. Wirth LJ, Allen AM, Posner MR, et al. Phase I dose-finding study of paclitaxel with panitumumab, carboplatin and intensity-modulated radiotherapy in patients with locally advanced squamous cell cancer of the head and neck. *Ann Oncol*. 2010;21(2):342–347.
 32. Bastholt L, Specht L, Jensen K, et al. A novel fully human monoclonal antibody against epidermal growth factor receptor (EGFR). First clinical and FDG-PET imaging results from a phase I/II trial conducted by the Danish Head and Neck Cancer Study Group (DAHANCA) in patients with squamous cell carcinoma of the head and neck (SCCHN) [Meeting Abstracts]. *J Clin Oncol*. 2005;23(16 suppl):5530.
 33. Bastholt L, Specht L, Jensen K, et al. Phase I/II clinical and pharmacokinetic study evaluating a fully human monoclonal antibody against EGFR (HuMax-EGFR) in patients with advanced squamous cell carcinoma of the head and neck. *Radiother Oncol*. 2007;85(1):24–28.
 34. Crombet T, Osorio M, Cruz T, et al. Use of the humanized anti-epidermal growth factor receptor monoclonal antibody h-R3 in combination with radiotherapy in the treatment of locally advanced head and neck cancer patients. *J Clin Oncol*. 2004;22(9):1646–1654.
 35. Shenoy AM, Reddy BK, Vidyasagar M, et al. BioMab EGFRTM (nimotuzumab/H-r3) in combination with standard of care in squamous cell carcinoma of head and neck (SCCHN). Presented at the 7th International Conference on Head and Neck Cancer, San Francisco, CA, July 19–23, 2008.
 36. Talavera A, Friemann R, Gomez-Puerta S, et al. Nimotuzumab, an antitumor antibody that targets the epidermal growth factor receptor, blocks ligand binding while permitting the active receptor conformation. *Cancer Res*. 2009;69(14):5851–5859.
 37. Khan AJ, King BL, Smith BD, et al. Characterization of the HER-2/neu oncogene by immunohistochemical and fluorescence in situ hybridization analysis in oral and oropharyngeal squamous cell carcinoma. *Clin Cancer Res*. 2002;8(2):540–548.
 38. Klapper LN, Vaisman N, Hurwitz E, Pinkas-Kramarski R, Yarden Y, Sela M. A subclass of tumor-inhibitory monoclonal antibodies to ErbB-2/HER2 blocks crosstalk with growth factor receptors. *Oncogene*. 1997;14(17):2099–2109.
 39. Gillison ML, Glisson BS, O’Leary E, et al. Phase II trial of trastuzumab (T), paclitaxel (P) and cisplatin (C) in metastatic (M) or recurrent (R) head and neck squamous cell carcinoma (HNSCC): response by tumor EGFR and HER2/neu status [Meeting Abstracts]. *J Clin Oncol*. 2006;24(18 suppl):5511.
 40. Nabili V, Tan JW, Bhuta S, Sercarz JA, Head CS. Salivary duct carcinoma: a clinical and histologic review with implications for trastuzumab therapy. *Head Neck*. 2007;29(10):907–912.
 41. Prat A, Parera M, Reyes V, et al. Successful treatment of pulmonary metastatic salivary ductal carcinoma with trastuzumab-based therapy. *Head Neck*. 2008;30(5):680–683.
 42. Cohen EEW, Rosen F, Stadler WM, et al. Phase II trial of ZD1839 in recurrent or metastatic squamous cell carcinoma of the head and neck. *J Clin Oncol*. 2003;21(10):1980–1987.
 43. Kirby AM, A’Hern RP, D’Ambrosio C, et al. Gefitinib (ZD1839, Iressa) as palliative treatment in recurrent or metastatic head and neck cancer. *Br J Cancer*. 2006;94(5):631–636.

44. Wheeler RH, Jones D, Sharma P, et al. Clinical and molecular phase II study of gefitinib in patients (pts) with recurrent squamous cell cancer of the head and neck (H&N Ca) [Meeting Abstracts]. *J Clin Oncol*. 2005;23(16 suppl):5531.
45. Cohen EE, Kane MA, List MA, et al. Phase II trial of gefitinib 250 mg daily in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck. *Clin Cancer Res*. 2005;11(23):8418–8424.
46. Stewart JS, Cohen EE, Licitra L, et al. Phase III study of gefitinib 250 compared with intravenous methotrexate for recurrent squamous cell carcinoma of the head and neck. *J Clin Oncol*. 2009;27(11):1864–1871.
47. Argiris A, Ghebremichael M, Gilbert J, Burtress B, Forastiere A. A phase III randomized, placebo-controlled trial of docetaxel (D) with or without gefitinib (G) in recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN): a trial of the Eastern Cooperative Oncology Group (ECOG) [Meeting Abstracts]. *J Clin Oncol*. 2009;27(15S):6011.
48. Soulieres D, Senzer NN, Vokes EE, Hidalgo M, Agarwala SS, Siu LL. Multicenter phase II study of erlotinib, an oral epidermal growth factor receptor tyrosine kinase inhibitor, in patients with recurrent or metastatic squamous cell cancer of the head and neck. *J Clin Oncol*. 2004;22(1):77–85.
49. Siu LL, Soulieres D, Chen EX, et al. Phase I/II trial of erlotinib and cisplatin in patients with recurrent or metastatic squamous cell carcinoma of the head and neck: a Princess Margaret Hospital Phase II consortium and National Cancer Institute of Canada Clinical Trials Group Study. *J Clin Oncol*. 2007;25(16):2178–2183.
50. Abidoye OO, Cohen EE, Wong SJ, et al. A phase II study of lapatinib (GW572016) in recurrent/metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN) [Meeting Abstracts]. *J Clin Oncol*. 2006;24(18 suppl):5568.
51. Baserga R, Peruzzi F, Reiss K. The IGF-1 receptor in cancer biology. *Int J Cancer*. 2003;107(6):873–877.
52. Pollak M. Insulin and insulin-like growth factor signalling in neoplasia. *Nat Rev Cancer*. 2008;8(12):915–928.
53. Barnes CJ, Ohshiro K, Rayala SK, El-Naggar AK, Kumar R. Insulin-like Growth Factor Receptor as a Therapeutic Target in Head and Neck Cancer. *Clin Cancer Res*. 2007;13(14):4291–4299.
54. Jun H, Chang M, Ko Y, et al. Clinical significance of type 1 insulin-like growth factor receptor and insulin-like growth factor binding protein-3 expression in squamous cell carcinoma of head and neck [Meeting Abstracts]. *J Clin Oncol*. 2009;27(15S):6036.
55. Vincent AM, Feldman EL. Control of cell survival by IGF signaling pathways. *Growth Horm IGF Res*. 2002;12(4):193–197.
56. Morgillo F, Kim WY, Kim ES, Ciardiello F, Hong WK, Lee HY. Implication of the insulin-like growth factor-IR pathway in the resistance of non-small cell lung cancer cells to treatment with gefitinib. *Clin Cancer Res*. 2007;13(9):2795–2803.
57. Morgillo F, Woo JK, Kim ES, Hong WK, Lee HY. Heterodimerization of insulin-like growth factor receptor/epidermal growth factor receptor and induction of survivin expression counteract the antitumor action of erlotinib. *Cancer Res*. 2006;66(20):10100–10111.
58. Di Renzo MF, Narsimhan RP, Olivero M, et al. Expression of the Met/HGF receptor in normal and neoplastic human tissues. *Oncogene*. 1991;6(11):1997–2003.
59. Bottaro DP, Rubin JS, Faletto DL, et al. Identification of the hepatocyte growth factor receptor as the c-met proto-oncogene product. *Science*. 1991;251(4995):802–804.
60. Boccaccio C, Ando M, Tamagnone L, et al. Induction of epithelial tubules by growth factor HGF depends on the STAT pathway. *Nature*. 1998;391(6664):285–288.
61. Hartmann G, Weidner KM, Schwarz H, Birchmeier W. The motility signal of scatter factor/hepatocyte growth factor mediated through the receptor tyrosine kinase met requires intracellular action of Ras. *J Biol Chem*. 1994;269(35):21936–21939.
62. Graziani A, Gramaglia D, Cantley LC, Comoglio PM. The tyrosine-phosphorylated hepatocyte growth factor/scatter factor receptor associates with phosphatidylinositol 3-kinase. *J Biol Chem*. 1991;266(33):22087–22090.
63. Ma PC, Maulik G, Christensen J, Sargia R. c-Met: structure, functions and potential for therapeutic inhibition. *Cancer Metastasis Rev*. 2003;22(4):309–325.
64. Peruzzi B, Bottaro DP. Targeting the c-Met signaling pathway in cancer. *Clin Cancer Res*. 2006;12(12):3657–3660.
65. Birchmeier C, Birchmeier W, Gherardi E, Vande Woude GF. Met, metastasis, motility and more. *Nat Rev Mol Cell Biol*. 2003;4(12):915–925.
66. Ma PC, Tretiakova MS, MacKinnon AC, et al. Expression and mutational analysis of MET in

- human solid cancers. *Genes, Chromosomes and Cancer*. 2008; 47(12):1025–1037.
67. Chen YS, Wang JT, Chang YF, et al. Expression of hepatocyte growth factor and c-met protein is significantly associated with the progression of oral squamous cell carcinoma in Taiwan. *J Oral Pathol Med*. 2004;33(4):209–217.
 68. Lo Muzio L, Leonardi R, Mignogna MD, et al. Scatter factor receptor (c-Met) as possible prognostic factor in patients with oral squamous cell carcinoma. *Anticancer Res*. 2004;24(2C):1063–1069.
 69. Murai M, Shen X, Huang L, et al. Overexpression of c-met in oral SCC promotes hepatocyte growth factor-induced disruption of cadherin junctions and invasion. *Int J Oncol*. 2004;25(4):831–840.
 70. Knowles LM, Stabile LP, Egloff AM, et al. HGF and c-Met participate in paracrine tumorigenic pathways in head and neck squamous cell cancer. *Clin Cancer Res*. 2009;15(11):3740–3750.
 71. Cortesina G, Martone T, Galeazzi E, et al. Staging of head and neck squamous cell carcinoma using the MET oncogene product as marker of tumor cells in lymph node metastases. *Int J Cancer*. 2000; 89(3):286–292.
 72. Yucel OT, Sungur A, Kaya S. c-met overexpression in supraglottic laryngeal squamous cell carcinoma and its relation to lymph node metastases. *Otolaryngol Head Neck Surg*. 2004;130(6):698–703.
 73. Salgia R. Role of c-Met in cancer: emphasis on lung cancer. *Semin Oncol*. 2009;36(2 suppl 1):S52–S58.
 74. Kwak EL, Camidge DR, Clark J, et al. Clinical activity observed in a phase I dose escalation trial of an oral c-met and ALK inhibitor, PF-02341066 [Meeting Abstracts]. *J Clin Oncol*. 2009;27(15S):3509.
 75. Kim ES, Salgia R. MET pathway as a therapeutic target. *J Thorac Oncol*. 2009;4(4):444–447.
 76. Zou HY, Li Q, Lee JH, et al. An orally available small-molecule inhibitor of c-Met, PF-2341066, exhibits cytoreductive antitumor efficacy through antiproliferative and antiangiogenic mechanisms. *Cancer Res*. 2007;67(9):4408–4417.
 77. Seiwert TY, Jagadeeswaran R, Faoro L, et al. The MET receptor tyrosine kinase is a potential novel therapeutic target for head and neck squamous cell carcinoma. *Cancer Res*. 2009;69(7):3021–3031.
 78. Sridhar SS, Hedley D, Siu LL. Raf kinase as a target for anticancer therapeutics. *Mol Cancer Ther*. 2005;4(4):677–685.
 79. Beeram M, Patnaik A, Rowinsky EK. Raf: a strategic target for therapeutic development against cancer. *J Clin Oncol*. 2005;23(27):6771–6790.
 80. Bissada E, Abou-Chakra Z, Weng X, et al. Prevalence of K-RAS codon 12 mutations in locally advanced head and neck squamous cell carcinoma and influence with regards to response to chemoradiation therapy [Meeting Abstracts]. *J Clin Oncol*. 2008;26 (15 suppl):17005.
 81. Hoa M, Davis SL, Ames SJ, Spanjaard RA. Amplification of wild-type K-ras promotes growth of head and neck squamous cell carcinoma. *Cancer Res*. 2002;62(24):7154–7156.
 82. Yarbrough WG, Shores C, Witsell DL, Weissler MC, Fidler ME, Gilmer TM. ras mutations and expression in head and neck squamous cell carcinomas. *Laryngoscope*. 1994;104(11 Pt 1):1337–1347.
 83. McDonald JS, Jones H, Pavelic ZP, Pavelic LJ, Stambrook PJ, Gluckman JL. Immunohistochemical detection of the H-ras, K-ras, and N-ras oncogenes in squamous cell carcinoma of the head and neck. *J Oral Pathol Med*. 1994;23(8):342–346.
 84. Saranath D, Chang SE, Bhoite LT, et al. High frequency mutation in codons 12 and 61 of H-ras oncogene in chewing tobacco-related human oral carcinoma in India. *Br J Cancer*. 1991;63(4):573–578.
 85. Saranath D, Panchal RG, Nair R, et al. Oncogene amplification in squamous cell carcinoma of the oral cavity. *Jpn J Cancer Res*. 1989;80(5):430–437.
 86. Wilhelm S, Carter C, Lynch M, et al. Discovery and development of sorafenib: a multikinase inhibitor for treating cancer. *Nat Rev Drug Discov*. 2006; 5(10):835–844.
 87. Williamson SK, Moon J, Huang CH, Guaglianone P, Wolf GT, Urba SG. A phase II trial of sorafenib in patients with recurrent and/or metastatic head and neck squamous cell carcinoma (HNSCC): a Southwest Oncology Group (SWOG) trial [Meeting Abstracts]. *J Clin Oncol*. 2007;25(18 suppl):6044.
 88. Elser C, Siu LL, Winkquist E, et al. Phase II trial of sorafenib in patients with recurrent or metastatic squamous cell carcinoma of the head and neck or nasopharyngeal carcinoma. *J Clin Oncol*. 2007;25(24):3766–3773.
 89. Choong NW, Kozloff M, Taber D, et al. Phase II study of sunitinib malate in head and neck squamous cell carcinoma. *Invest New Drugs*. 2010 Oct;28(5): 677–683.
 90. Fountzilas G, Fragkoulidi A, Kalogera-Fountzila A, et al. A phase II study of sunitinib in patients with recurrent and/or metastatic non-nasopharyngeal head and neck cancer. *Cancer Chemother Pharmacol*. 2009; 65(4):649–660.
 91. Machiels J-PH, Henry S, Zanetta S, et al. Phase II study of sunitinib in recurrent or metastatic

- squamous cell carcinoma of the head and neck: GORTEC 2006-01. *J Clin Oncol*. 2010;28(1):21–28.
92. Amornphimoltham P, Sriuranpong V, Patel V, et al. Persistent activation of the Akt pathway in head and neck squamous cell carcinoma: a potential target for UCN-01. *Clin Cancer Res*. 2004;10(12 Pt 1):4029–4037.
93. Bussink J, van der Kogel AJ, Kaanders JH. Activation of the PI3-K/AKT pathway and implications for radioresistance mechanisms in head and neck cancer. *Lancet Oncol*. 2008;9(3):288–296.
94. Worsham MJ, Pals G, Schouten JP, et al. Delineating genetic pathways of disease progression in head and neck squamous cell carcinoma. *Arch Otolaryngol Head Neck Surg*. 2003;129(7):702–708.
95. Lothaire P, Azambuja Ed, Dequanter D, et al. Molecular markers of head and neck squamous cell carcinoma: promising signs in need of prospective evaluation. *Head & Neck*. 2006;28(3):256–269.
96. Pedrero JMG, Carracedo DG, Pinto CM, et al. Frequent genetic and biochemical alterations of the PI 3-K/AKT/PTEN pathway in head and neck squamous cell carcinoma. *Int J Cancer*. 2005;114(2):242–248.
97. West KA, Brognard J, Clark AS, et al. Rapid Akt activation by nicotine and a tobacco carcinogen modulates the phenotype of normal human airway epithelial cells. *J Clin Invest*. 2003;111(1):81–90.
98. Massarelli E, Liu DD, Lee JJ, et al. Akt activation correlates with adverse outcome in tongue cancer. *Cancer*. 2005;104(11):2430–2436.
99. Argiris A, Cohen E, Karrison T, et al. A phase II trial of perifosine, an oral alkylphospholipid, in recurrent or metastatic head and neck cancer. *Cancer Biol Ther*. 2006;5(7):766–770.
100. Janmaat ML, Kruij FAE, Rodriguez JA, Giaccone G. Response to epidermal growth factor receptor inhibitors in non-small cell lung cancer cells. *Clin Cancer Res*. 2003;9(6):2316–2326.
101. Sarbassov DD, Ali SM, Sengupta S, et al. Prolonged rapamycin treatment inhibits mTORC2 assembly and Akt/PKB. *Mol Cell*. 2006;22(2):159–168.
102. Wullschlegel S, Loewith R, Hall MN. TOR signaling in growth and metabolism. *Cell*. 2006;124(3):471–484.
103. Beretta L, Gingras AC, Svitkin YV, Hall MN, Sonenberg N. Rapamycin blocks the phosphorylation of 4E-BP1 and inhibits cap-dependent initiation of translation. *EMBO J*. 1996;15(3):658–664.
104. Jastrzebski K, Hannan KM, Tchoubrieva EB, Hannan RD, Pearson RB. Coordinate regulation of ribosome biogenesis and function by the ribosomal protein S6 kinase, a key mediator of mTOR function. *Growth Factors*. 2007;25(4):209–226.
105. Meric-Bernstam F, Gonzalez-Angulo AM. Targeting the mTOR Signaling Network for Cancer Therapy. *J Clin Oncol*. 2009;27(13):2278–2287.
106. Mita MM, Mita AC, Chu QS, et al. Phase I trial of the novel mammalian target of rapamycin inhibitor deforolimus (AP23573; MK-8669) administered intravenously daily for 5 days every 2 weeks to patients with advanced malignancies. *J Clin Oncol*. 2008;26(3):361–367.
107. Perotti A, Maur M, Vigano L, et al. Phase Ib pharmacokinetic (PK) and pharmacodynamic (PD) study to define the optimal dose for combining the mTOR inhibitor AP23573 with capecitabine (CAPE) [Meeting Abstracts]. *J Clin Oncol*. 2006;24(18 suppl):3065.
108. Figlin RA, Brown E, Armstrong AJ, et al. NCCN Task Force Report: mTOR inhibition in solid tumors. *J Natl Compr Canc Netw*. 2008;6(suppl 5):S1–S20; quiz S21–S22.
109. Shah OJ, Wang Z, Hunter T. Inappropriate activation of the TSC/Rheb/mTOR/S6K cassette induces IRS1/2 depletion, insulin resistance, and cell survival deficiencies. *Curr Biol*. 2004;14(18):1650–1656.
110. Harrington LS, Findlay GM, Lamb RF. Restraining PI3K: mTOR signalling goes back to the membrane. *Trends Biochem Sci*. 2005;30(1):35–42.
111. Hay N. The Akt-mTOR tango and its relevance to cancer. *Cancer Cell*. 2005;8(3):179–183.
112. Oh SH, Kim WY, Kim JH, et al. Identification of insulin-like growth factor binding protein-3 as a farnesyl transferase inhibitor SCH66336-induced negative regulator of angiogenesis in head and neck squamous cell carcinoma. *Clin Cancer Res*. 2006;12(2):653–661.
113. Carter CA, Kane CJ. Therapeutic potential of natural compounds that regulate the activity of protein kinase C. *Curr Med Chem*. 2004;11(21):2883–2902.
114. Cohen EEW, Lingen MW, Zhu B, et al. Protein Kinase C{zeta} Mediates Epidermal Growth Factor-Induced Growth of Head and Neck Tumor Cells by Regulating Mitogen-Activated Protein Kinase. *Cancer Res*. 2006;66(12):6296–6303.
115. Sebt SM, Adjei AA. Farnesyltransferase inhibitors. *Semin Oncol*. 2004;31(suppl 1):28–39.
116. Mantha A, McFee K, Niknejad N, Goss G, Lorimer I, Dimitroulakos J. Epidermal growth factor receptor-targeted therapy potentiates lovastatin-induced apoptosis in head and neck squamous cell carcinoma cells. *J Cancer Res Clin Oncol*. 2003;129(11):631–641.

117. Yang CH, Kies MS, Glisson B, et al. A phase II study of Ionafarnib (SCH66336) in patients with chemorefractory advanced head and neck squamous cell carcinoma (HNSCC) [Meeting Abstracts]. *J Clin Oncol*. 2005;23(16 suppl):5565-.
118. Summy JM, Gallick GE. Src family kinases in tumor progression and metastasis. *Cancer Metastasis Rev*. 2003;22(4):337-358.
119. Belsches AP, Haskell MD, Parsons SJ. Role of c-Src tyrosine kinase in EGF-induced mitogenesis. *Front Biosci*. 1997;2:d501-d518.
120. Maa MC, Leu TH, McCarley DJ, Schatzman RC, Parsons SJ. Potentiation of epidermal growth factor receptor-mediated oncogenesis by c-Src: implications for the etiology of multiple human cancers. *Proc Natl Acad Sci U S A*. 1995;92(15):6981-6985.
121. Tice DA, Biscardi JS, Nickles AL, Parsons SJ. Mechanism of biological synergy between cellular Src and epidermal growth factor receptor. *Proc Natl Acad Sci U S A*. 1999;96(4):1415-1420.
122. Xi S, Zhang Q, Dyer KF, et al. Src kinases mediate STAT growth pathways in squamous cell carcinoma of the head and neck. *J Biol Chem*. 2003;278(34):31574-31583.
123. Yang Z, Bagheri-Yarmand R, Wang RA, et al. The epidermal growth factor receptor tyrosine kinase inhibitor ZD1839 (Iressa) suppresses c-Src and Pak1 pathways and invasiveness of human cancer cells. *Clin Cancer Res*. 2004;10(2):658-667.
124. Lombardo LJ, Lee FY, Chen R, et al. Discovery of N-(2-chloro-6-methyl-phenyl)-2-(6-(4-(2-hydroxyethyl)-piperazin-1-yl)-2-methylpyrimidin-4-ylamino)thiazole-5-carboxamide (BMS-354825), a dual Src/Abl kinase inhibitor with potent antitumor activity in pre-clinical assays. *J Med Chem*. 2004;47(27):6658-6661.
125. Brooks HD, Glisson B, Lu C, et al. Phase II study of dasatinib in the treatment of head and neck squamous cell carcinoma (HNSCC) [Meeting Abstracts]. *J Clin Oncol*. 2009;27(15S):6022.
126. Lingen MW, Polverini PJ, Bouck NP. Inhibition of squamous cell carcinoma angiogenesis by direct interaction of retinoic acid with endothelial cells. *Lab Invest*. 1996;74(2):476-483.
127. Petruzzelli GJ, Benefield J, Taitz AD, et al. Heparin-binding growth factor(s) derived from head and neck squamous cell carcinomas induce endothelial cell proliferations. *Head Neck*. 1997;19(7):576-582.
128. Semenza GL. Targeting HIF-1 for cancer therapy. *Nat Rev Cancer*. 2003;3(10):721-732.
129. O-charoenrat P, Rhys-Evans P, Modjtahedi H, Eccles SA. Vascular endothelial growth factor family members are differentially regulated by c-erbB signaling in head and neck squamous carcinoma cells. *Clin Exp Metastasis*. 2000;18(2):155-161.
130. Vilorio-Petit A, Crombet T, Jothy S, et al. Acquired resistance to the antitumor effect of epidermal growth factor receptor-blocking antibodies in vivo: a role for altered tumor angiogenesis. *Cancer Res*. 2001;61(13):5090-5101.
131. Jain RK. Tumor angiogenesis and accessibility: role of vascular endothelial growth factor. *Semin Oncol*. 2002;29(6 suppl 16):3-9.
132. Cohen EE, Davis DW, Karrison TG, et al. Erlotinib and bevacizumab in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck: a phase I/II study. *Lancet Oncol*. 2009;10(3):247-257.
133. Kies MS, Gibson MK, Kim SW, et al. Cetuximab (C) and bevacizumab (B) in patients with recurrent or metastatic head and neck squamous cell carcinoma (SCCHN): an interim analysis [Meeting Abstracts]. *J Clin Oncol*. 2008;26(15 suppl):6072.
134. Gibson MK, Kies M, Kim S, et al. Cetuximab (C) and bevacizumab (B) in patients with recurrent or metastatic head and neck squamous cell carcinoma: an updated report [Meeting Abstracts]. *J Clin Oncol*. 2009;27(15S):6049.
135. Feinstein TM, Raez LE, Rajasenan KK, et al. Pemetrexed (P) and bevacizumab (B) in patients (pts) with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC): updated results of a phase II trial [Meeting Abstracts]. *J Clin Oncol*. 2008;26(15)(suppl):6069.
136. Fury M, Zahalsky A, Wong R, et al. A Phase II study of SU5416 in patients with advanced or recurrent head and neck cancers. *Invest New Drugs*. 2007;25(2):165-172.
137. Ferrara N, Gerber HP, LeCouter J. The biology of VEGF and its receptors. *Nat Med*. 2003;9(6):669-676.
138. Sano D, Kawakami M, Fujita K, et al. Antitumor effects of ZD6474 on head and neck squamous cell carcinoma. *Oncol Rep*. February 2007;17(2):289-295.
139. Saura C, Baselga J, Herbst R, et al. Antitumor activity of cediranib in patients with metastatic or recurrent head and neck cancer (HNC) or recurrent non-small cell lung cancer (NSCLC): an open-label exploratory study [Meeting Abstracts]. *J Clin Oncol*. 2009;27(15S):6023.
140. Fu J, Bian M, Jiang Q, Zhang C. Roles of Aurora kinases in mitosis and tumorigenesis. *Mol Cancer Res*. 2007;5(1):1-10.
141. Carvajal RD, Tse A, Schwartz GK. Aurora kinases: new targets for cancer therapy. *Clin Cancer Res*. 2006;12(23):6869-6875.

142. Reiter R, Gais P, Jutting U, et al. Aurora kinase a messenger RNA overexpression is correlated with tumor progression and shortened survival in head and neck squamous cell carcinoma. *Clin Cancer Res*. 2006;12(17):5136–5141.
143. Qi G, Ogawa I, Kudo Y, et al. Aurora-B expression and its correlation with cell proliferation and metastasis in oral cancer. *Virchows Arch*. 2007;450(3):297–302.
144. Gautschi O, Heighway J, Mack PC, Purnell PR, Lara PN Jr, Gandara DR. Aurora kinases as anticancer drug targets. *Clinical Cancer Res*. 2008;14(6):1639–1648.
145. Boss DS, Beijnen JH, Schellens JHM. Clinical experience with aurora kinase inhibitors: a review. *Oncologist*. 2009;14(8):780–793.
146. Shapiro GI. Cyclin-dependent kinase pathways as targets for cancer treatment. *J Clin Oncol*. 2006;24(11):1770–1783.
147. Patel V, Senderowicz AM, Pinto D, et al. Flavopiridol, a novel cyclin-dependent kinase inhibitor, suppresses the growth of head and neck squamous cell carcinomas by inducing apoptosis. *J Clin Invest*. 1998;102(9):1674–1681.
148. Tan AR, Headlee D, Messmann R, et al. Phase I clinical and pharmacokinetic study of flavopiridol administered as a daily 1-hour infusion in patients with advanced neoplasms. *J Clin Oncol*. 2002;20(19):4074–4082.
149. Thomas JP, Tutsch KD, Cleary JF, et al. Phase I clinical and pharmacokinetic trial of the cyclin-dependent kinase inhibitor flavopiridol. *Cancer Chemother Pharmacol*. 2002;50(6):465–472.
150. Mihara M, Shintani S, Kiyota A, Matsumura T, Wong DT. Cyclin-dependent kinase inhibitor (ros-covitine) suppresses growth and induces apoptosis by regulating Bcl-x in head and neck squamous cell carcinoma cells. *Int J Oncol*. 2002;21(1):95–101.
151. Yeo W, Goh B, Le Tourneau C, Green SR, Chiao JH, Siu LL. A phase II randomized study of oral seliciclib in patients with previously treated nasopharyngeal carcinoma [Meeting Abstracts]. *J Clin Oncol*. 2009;27(15S):6026.
152. Patel V, Lahusen T, Leethanakul C, et al. Antitumor activity of UCN-01 in carcinomas of the head and neck is associated with altered expression of cyclin D3 and p27(KIP1). *Clin Cancer Res*. 2002;8(11):3549–3560.
153. Sato S, Fujita N, Tsuruo T. Interference with PDK1-Akt survival signaling pathway by UCN-01 (7-hydroxystaurosporine). *Oncogene*. 2002;21(11):1727–1738.
154. Adams J, Palombella VJ, Sausville EA, et al. Proteasome inhibitors: a novel class of potent and effective antitumor agents. *Cancer Res*. 1999;59(11):2615–2622.
155. Russo A, Fratto ME, Bazan V, et al. Targeting apoptosis in solid tumors: the role of bortezomib from preclinical to clinical evidence. *Expert Opinion on Ther Targets*. 2007;11(12):1571–1586.
156. Aggarwal BB. Nuclear factor-kappaB: the enemy within. *Cancer Cell*. 2004;6(3):203–208.
157. Allen C, Saigal K, Nottingham L, Arun P, Chen Z, Van Waes C. Bortezomib-induced apoptosis with limited clinical response is accompanied by inhibition of canonical but not alternative nuclear factor-[kappa]B subunits in head and neck cancer. *Clin Cancer Res*. 2008;14(13):4175–4185.
158. Bancroft CC, Chen Z, Yeh J, et al. Effects of pharmacologic antagonists of epidermal growth factor receptor, PI3K and MEK signal kinases on NF-kappaB and AP-1 activation and IL-8 and VEGF expression in human head and neck squamous cell carcinoma lines. *Int J Cancer*. 2002;99(4):538–548.
159. Ondrey FG, Dong G, Sunwoo J, et al. Constitutive activation of transcription factors NF-(kappa)B, AP-1, and NF-IL6 in human head and neck squamous cell carcinoma cell lines that express pro-inflammatory and pro-angiogenic cytokines. *Mol Carcinog*. 1999;26(2):119–129.
160. Voorhees PM, Dees EC, O'Neil B, Orlowski RZ. The proteasome as a target for cancer therapy. *Clin Cancer Res*. 2003;9(17):6316–6325.
161. Salvat C, Aquaviva C, Jariel-Encontre I, et al. Are there multiple proteolytic pathways contributing to c-Fos, c-Jun and p53 protein degradation in vivo? *Mol Biol Rep*. 1999;26(1–2):45–51.
162. Li B, Dou QP. Bax degradation by the ubiquitin/proteasome-dependent pathway: involvement in tumor survival and progression. *Proc Natl Acad Sci U S A*. 2000;97(8):3850–3855.
163. Dent P, Jarvis WD, Birrer MJ, Fisher PB, Schmidt-Ullrich RK, Grant S. The roles of signaling by the p42/p44 mitogen-activated protein (MAP) kinase pathway; a potential route to radio- and chemosensitization of tumor cells resulting in the induction of apoptosis and loss of clonogenicity. *Leukemia*. 1998;12(12):1843–1850.
164. Kubicek GJ, Machtay M, Axelrod RA, et al. Phase I trial of bortezomib (VELCADE), cisplatin and radiotherapy for advanced head and neck cancer [Meeting Abstracts]. *J Clin Oncol*. 2008;26(15 suppl):6028.
165. Morimoto RI, Kline MP, Bimston DN, Cotto JJ. The heat-shock response: regulation and function of heat-shock proteins and molecular chaperones. *Essays Biochem*. 1997;32:17–29.

166. Welch WJ, Feramisco JR. Purification of the major mammalian heat shock proteins. *J Biol Chem*. 1982;257(24):14949–14959.
167. Banerji U. Heat shock protein 90 as a drug target: some like it hot. *Clin Cancer Res*. 2009;15(1):9–14.
168. Connell P, Ballinger CA, Jiang J, et al. The co-chaperone CHIP regulates protein triage decisions mediated by heat-shock proteins. *Nat Cell Biol*. 2001;3(1):93–96.
169. Yin X, Zhang H, Burrows F, Zhang L, Shores CG. Potent activity of a novel dimeric heat shock protein 90 inhibitor against head and neck squamous cell carcinoma in vitro and in vivo. *Clin Cancer Res*. 2005;11(10):3889–3896.
170. Ferrarini M, Heltai S, Zocchi MR, Rugarli C. Unusual expression and localization of heat-shock proteins in human tumor cells. *Int J Cancer*. 1992;51(4):613–619.
171. Bull EE, Dote H, Brady KJ, et al. Enhanced tumor cell radiosensitivity and abrogation of G2 and S phase arrest by the Hsp90 inhibitor 17-(dimethylaminoethylamino)-17-demethoxygeldanamycin. *Clin Cancer Res*. 2004;10(23):8077–8084.
172. Russell JS, Burgan W, Oswald KA, Camphausen K, Tofilon PJ. Enhanced cell killing induced by the combination of radiation and the heat shock protein 90 inhibitor 17-allylamino-17-demethoxygeldanamycin: a multitarget approach to radiosensitization. *Clin Cancer Res*. 2003;9(10 Pt 1):3749–3755.
173. Papadimitrakopoulou VA, Fiorentino S, Naemuddin M. Potent activity of the heat shock protein 90 (Hsp90) inhibitor, 17AAG in head and neck squamous cell carcinoma (HNSCC) lines [Meeting Abstracts]. *AACR*. 2006;2006(1):1104b.
174. Ramanathan RK, Trump DL, Eiseman JL, et al. Phase I pharmacokinetic-pharmacodynamic study of 17-(allylamino)-17-demethoxygeldanamycin (17AAG, NSC 330507), a novel inhibitor of heat shock protein 90, in patients with refractory advanced cancers. *Clin Cancer Res*. 2005;11(9):3385–3391.
175. Workman P. Auditing the pharmacological accounts for Hsp90 molecular chaperone inhibitors: unfolding the relationship between pharmacokinetics and pharmacodynamics. *Mol Cancer Ther*. 2003;2(2):131–138.
176. Yin X, Zhang H, Lundgren K, Wilson L, Burrows F, Shores CG. BIIB021, a novel Hsp90 inhibitor, sensitizes head and neck squamous cell carcinoma to radiotherapy. *Int J Cancer*. 2010;126:1216–1225.
177. Laird PW. Cancer epigenetics. *Hum Mol Genet*. 2005;14(Spec No 1):R65–R76.
178. Egger G, Liang G, Aparicio A, Jones PA. Epigenetics in human disease and prospects for epigenetic therapy. *Nature*. 2004;429(6990):457–463.
179. Johnstone RW. Histone-deacetylase inhibitors: novel drugs for the treatment of cancer. *Nat Rev Drug Discov*. 2002;1(4):287–299.
180. Gregory PD, Wagner K, Horz W. Histone acetylation and chromatin remodeling. *Exp Cell Res*. 2001;265(2):195–202.
181. Marks PA, Rifkind RA, Richon VM, Breslow R, Miller T, Kelly WK. Histone deacetylases and cancer: causes and therapies. *Nat Rev Cancer*. 2001;1(3):194–202.
182. Kim TY, Bang YJ, Robertson KD. Histone deacetylase inhibitors for cancer therapy. *Epigenetics*. 2006;1(1):14–23.
183. Sakuma T, Uzawa K, Onda T, et al. Aberrant expression of histone deacetylase 6 in oral squamous cell carcinoma. *Int J Oncol*. 2006;29(1):117–124.
184. Lee M-J, Kim YS, Kummur S, Giaccone G, Trepel JB. Histone deacetylase inhibitors in cancer therapy. *Current Opinion in Oncology*. 2008;20(6):639–649.
185. Duan J, Friedman J, Nottingham L, Chen Z, Ara G, Van Waes C. Nuclear factor-kappaB p65 small interfering RNA or proteasome inhibitor bortezomib sensitizes head and neck squamous cell carcinomas to classic histone deacetylase inhibitors and novel histone deacetylase inhibitor PXD101. *Mol Cancer Ther*. 2007;6(1):37–50.
186. Gillenwater AM, Zhong M, Lotan R. Histone deacetylase inhibitor suberoylanilide hydroxamic acid induces apoptosis through both mitochondrial and Fas (Cd95) signaling in head and neck squamous carcinoma cells. *Mol Cancer Ther*. 2007;6(11):2967–2975.
187. Ramalingam SS, Parise RA, Ramanathan RK, et al. Phase I and pharmacokinetic study of vorinostat, a histone deacetylase inhibitor, in combination with carboplatin and paclitaxel for advanced solid malignancies. *Clin Cancer Res*. June 15 2007;13(12):3605–3610.
188. Blumenschein G Jr, Kies M, Papadimitrakopoulou V, et al. Phase II trial of the histone deacetylase inhibitor vorinostat (Zolinza™, suberoylanilide hydroxamic acid, SAHA) in patients with recurrent and/or metastatic head and neck cancer. *Invest New Drugs*. 2008;26(1):81–87.
189. Chan G, Boyle JO, Yang EK, et al. Cyclooxygenase-2 Expression Is Up-Regulated in Squamous Cell Carcinoma of the Head and Neck. *Cancer Res*. 1999;59(5):991–994.

190. Williams CS, Tsujii M, Reese J, Dey SK, DuBois RN. Host cyclooxygenase-2 modulates carcinoma growth. *J Clin Invest*. 2000;105(11):1589–1594.
191. Jones MK, Wang H, Peskar BM, et al. Inhibition of angiogenesis by nonsteroidal anti-inflammatory drugs: insight into mechanisms and implications for cancer growth and ulcer healing. *Nat Med*. 1999;5(12):1418–1423.
192. Shiotani H, Denda A, Yamamoto K, et al. Increased expression of cyclooxygenase-2 protein in 4-nitroquinoline-1-oxide-induced rat tongue carcinomas and chemopreventive efficacy of a specific inhibitor, nimesulide. *Cancer Res*. 2001;61(4):1451–1456.
193. Nishimura G, Yanoma S, Satake K, et al. An experimental model of tumor dormancy therapy for advanced head and neck carcinoma. *Jpn J Cancer Res*. 2000;91(11):1199–1203.
194. Kishi K, Petersen S, Petersen C, et al. Preferential enhancement of tumor radioresponse by a cyclooxygenase-2 inhibitor. *Cancer Res*. 2000;60(5):1326–1331.
195. Petersen C, Petersen S, Milas L, Lang FF, Tofilon PJ. Enhancement of intrinsic tumor cell radiosensitivity induced by a selective cyclooxygenase-2 inhibitor. *Clin Cancer Res*. 2000;6(6):2513–2520.
196. Wirth LJ, Haddad RI, Lindeman NI, et al. Phase I study of gefitinib plus celecoxib in recurrent or metastatic squamous cell carcinoma of the head and neck. *J Clin Oncol*. 2005;23(28):6976–6981.
197. Dannenberg AJ, Lippman SM, Mann JR, Subbaramaiah K, DuBois RN. Cyclooxygenase-2 and epidermal growth factor receptor: pharmacologic targets for chemoprevention. *J Clin Oncol*. 2005;23(2):254–266.
198. Choe MS, Chen Z, Klass CM, Zhang X, Shin DM. Enhancement of docetaxel-induced cytotoxicity by blocking epidermal growth factor receptor and cyclooxygenase-2 pathways in squamous cell carcinoma of the head and neck. *Clin Cancer Res*. 2007;13(10):3015–3023.
199. Veronique JB, Michele R, Poirier GP. PARP-1, a determinant of cell survival in response to DNA damage. *Exp Hematol*. 2003;31(6):446–454.
200. Miknyoczki SJ, Jones-Bolin S, Pritchard S, et al. Chemopotential of temozolomide, irinotecan, and cisplatin activity by CEP-6800, a poly(ADP-Ribose) polymerase inhibitor. *Mol Cancer Ther*. 2003;2(4):371–382.
201. Jagtap P, Szabo C. Poly(ADP-ribose) polymerase and the therapeutic effects of its inhibitors. *Nat Rev Drug Discov*. 2005;4(5):421–440.
202. Khan K, Araki K, Wang D, et al. Head and neck cancer radiosensitization by the novel poly(ADP-ribose) polymerase inhibitor GPI-15427. *Head & Neck*. 2010;32(3):381–391.
203. Knoedler MK, Gauler T, Matzdorff A, et al. Multi-center phase II study of cetuximab plus docetaxel in 84 patients with recurrent or metastatic, platinum-pretreated SCCN [Meeting Abstracts]. *J Clin Oncol*. 2009;27(15S):6048.
204. Hitt R, Irigoyen A, Nunez J, et al. Phase II study of combination cetuximab and weekly paclitaxel in patients with metastatic/recurrent squamous cell carcinoma of head and neck (SCCHN): spanish head and neck cancer group (TTCC) [Meeting Abstracts]. *J Clin Oncol*. 2007;25(18 suppl):6012.

CHAPTER 4

Induction Chemotherapy in Locally Advanced Head and Neck Cancer: An Evolving Concept

Jochen H. Lorch

■ BACKGROUND

Squamous cell cancer of the head and neck (SCCHN) accounts for approximately 5% of newly diagnosed cancer and accounts for 644 000 cases and more than 350 000 cancer deaths worldwide each year (1). The majority of cases present with potentially curable locally advanced disease (LAHNC). Despite advances in the treatment of these patients, long-term disease-free and overall survival remains poor. Approximately 40% to 60% of patients develop local recurrences, and 20% to 30% will be diagnosed with distant metastatic disease (2).

Chemotherapy (CT) has emerged as an integral component in the management of locally advanced SCCHN in recent years. It has been used concurrently with radiation as chemoradiotherapy (CRT), as induction or neoadjuvant CT that is delivered before definitive locoregional treatment, or as adjuvant CT after conclusion of definitive local therapy. A large meta-analysis using data from 63 trials and a total of more than 10 000 patients treated with a variety of CT and radiation regimens has helped to establish the role of concomitant CT in locally advanced SCCHN (3). This analysis identified an 8% improvement in 5-year survival when CT was part of the CRT treatment regimen and a 5% improvement with

PF induction CT (Table 4.1). A follow-up analysis, which included an additional 23 trials for a total of more than 17 000 patients, confirmed a 5% benefit at 5 years in patients who had received PF induction CT as part of their regimen (4). Other randomized trials have solidified evidence that the addition of CT before or during radiation treatment with curative intent results in benefits in terms of organ preservation (5–7), longer time to disease progression (5–7,8–10), better locoregional control (11), fewer distant metastases (7,9), and longer overall survival times (8–13).

Induction CT is an attractive treatment option as it allows the assessment of tumor response and the selection of appropriate patients for organ preservation and improves local control while reducing the rate of distant metastases (14). Data from randomized trials in stage III and IV locally advanced laryngeal cancer patients have demonstrated that induction CT with cisplatin and 5-FU (PF) followed by radiation in cases when a response to the CT regimen can be achieved is equivalent to surgery and resulted in a 64% rate of organ preservation (5). Furthermore, data from European trials in the 1990s demonstrated promising results with high response rates to PF induction CT, a high rate of organ preservation, and at least a trend toward improved survival,

TABLE 4.1
Effects of chemotherapy on survival at 5 years: From the meta-analysis

Trial Category	No. of Trials	No. of Patients	Difference (%)	<i>P</i> value
All trials	65	10 850	+4	<.0001
Adjuvant	8	1854	+1	.74
Induction	31	5269	+2	.10
PF	15	2487	+5	.01
Other Chemo	16	2782	0	.91
Concomitant	26	3727	+8	<.0001

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particularly in patients with unresectable tumors (9,15). However, some clinicians felt discouraged by the modest 2% increase in survival demonstrated in the meta-analysis mentioned earlier in patients who received neoadjuvant CT (3). A closer look at the data, however, led to further insight, and there was some reason for optimism. Beyond the obvious limitations of a meta-analysis, this study included a wide variety of CT regimens, with numerous drug regimens and schedules that would be considered suboptimal by today's standards, limiting the applicability of the results to today's situation. Furthermore, the response to CT was not taken into account in this study. A subset analysis of cases in which the combination of a platinum with 5-FU (PF) had been used was associated with an overall 16% lower risk of death and a significant 5% survival benefit at 5 years. It has also been argued that this analysis may have underestimated the actual benefit, as the study included patients who underwent inappropriately timed surgical interventions between CT and radiation.

A randomized phase III organ preservation trial conducted by the European Organization for Research and Treatment of Cancer (EORTC) evaluated PF induction CT with definitive radiation versus standard surgery and radiation in patients with operable pyriform sinus cancer (6). Preservation of the larynx was possible in 42% of cases, and there was a lower rate of distant failures without a significant difference in survival. More

recently, the Intergroup 91-11 study compared induction CT, concurrent CRT, and radiation alone in patients with intermediate stage laryngeal cancer. The rate of larynx preservation favored concurrent CRT over induction CT. However, a recent long-term analysis from this trial reported that the long-term laryngectomy-free survival was equivalent in the CRT and the induction CT arms, and both were significantly superior to radiotherapy (RT) alone (16). Interestingly, the long-term survival data suggested a trend toward superior survival in the PF induction CT arm compared with CRT or RT alone. One of the issues of concern is the high rate of larynx preservation compared with laryngectomy-free survival suggesting an increased rate of death from toxicity—with preserved larynx—in the CRT arm.

Results from another randomized organ preservation trial were reported in which PF induction CT and RT were compared with alternating PF-based CRT in patients with resectable larynx and hypopharynx cancer (16). As in prior trials, induction CT with PF was equivalent for survival and organ preservation compared with CRT.

■ TAXANES

Definitive concomitant CRT has been the standard of care for patients with stage III and IV SCCHN who do not undergo surgical resection.

TABLE 4.2

Experience with docetaxel-based induction in locally advanced SCCHN

Study	n (Criteria)	Primary End Point	Regimens	Result
Vermorken 2007 (EORTC 24791/ TAX 323)	358 (unresectable)	PFS	PF → RT vs. TPF → RT	TPF led to higher PFS and OS ($P < .05$)
Posner, 2007 (TAX 324)	501 (Advanced)	OS	PF → CRT vs. TPF → CRT	TPF improved OS at 3 years ($P < .01$)
Calais 2006* (GORTEC 2000–2001)	213 (Resectable)	LxP	PF vs. TPF	TPF led to higher LxP, CR

* Preliminary results.

Induction CT, particularly in the United States, has remained the exception and has largely been restricted to research protocols. In recent years, the remarkable antitumor effect of taxanes in SCCHN has revived interest in induction CT. It was thought that by adding a taxane to the induction CT regimen, the already 60% to 90% overall response rate and 35% complete response rate seen with PF could be further increased resulting in more substantial clinical benefit. Several groups have tried to improve outcomes by incorporating taxanes in PF induction CT regimens. Data from phase I and II trials suggest that the combination of docetaxel with cisplatin and 5-FU (TPF) is safe and has a high rate of complete clinical and pathologic responses. Haddad et al reported a response rate of 80% to 100% with TPF induction CT followed by aggressive twice daily fractionated RT (17,18). The local failure rate was 31% and distant recurrences occurred at a remarkably low rate of 6%. All the distant recurrences were associated with locoregional failures. Thus, there was a 37% rate of local and distant failures with TPF, suggesting perhaps that induction CT followed by CRT could further reduce local recurrences and result in a lower risk for both local and distant recurrent disease.

Based on the extensive phase II data on induction TPF, 3 large randomized phase III trials were designed to explore whether the addition of docetaxel to PF induction CT could improve

outcomes compared with induction CT with PF alone (Table 4.2). In the Tax 323 study (Table 4.3), the regimen used in the experimental arm was based on studies conducted by Schrijvers et al (docetaxel 75 mg/m² on day 1, cisplatin 75 mg/m² on day 1, and 5-FU 750 mg/m² by continuous infusion for 5 days), which had demonstrated good safety and promising efficacy (19,20). The PF regimen consisted of the original Wayne State treatment plan, which included cisplatin 100 mg/m² and 5-FU 1000 mg/m² administered by continuous infusion on days 1 to 5. A total of 358 patients with unresectable, locally advanced SCCHN were enrolled, and 177 were randomized to receive TPF followed by RT while 181 underwent PF followed by RT. The end point of this trial was progression-free survival. With a median follow-up of 32.5 months, the median progression-free survival was 11 months in the TPF group versus 8.2 months in the control arm (hazard ratio [HR], 0.72; $P = .007$). Treatment with TPF resulted in a reduction in the risk of death by 27% ($P = .02$), with a median overall survival of 18.8 months compared with 14.5 months in the PF group. TPF was actually better tolerated with less grade 3 and 4 nausea (0.6% vs. 6.6%), vomiting (0.6% vs. 4.5%), mucositis (4.6% vs. 11.2%), less grade 3 hearing loss (0% vs. 2.8%), and less grade 3 and 4 thrombocytopenia (5.2% vs. 17.9%). There was a higher incidence of febrile neutropenia in patients on the TPF arm (76.9% vs. 52.5%), whereas the

TABLE 4.3

Survival results of TAX 323

	TPF-177	PF-181
PROGRESSION-FREE SURVIVAL		
Median duration (mo)	11.0	8.2
Hazard ratio	0.72 (CI 0.57–0.91)	—
Median survival (mo)	18.8	14.5
Hazard ratio	0.73 (CI 0.56–0.94)	
KAPLAN-MEIR SURVIVAL		
1-Year	72%	55%
2-Year	43%	32%
3-Year	37%	26%
RESPONSE TO INDUCTION CHEMOTHERAPY/INDUCTION PLUS CRT (%)		
Overall	68/72	54/59
Complete	15/59	12/36
Partial	105/69	85/70

number of treatment-related deaths was lower than that of the controls (2.3% vs. 5.5%).

A second phase III trial, the Tax 324 trial (Table 4.4), randomized 501 patients with resectable and unresectable SCCHN to TPF or PF followed by CRT with weekly carboplatin and daily RT (21). In this study, the primary end point was overall survival. The TPF regimen used was slightly more dose dense than the one tested in Tax 323, with a higher per cycle dose of cisplatin and 5-FU (TPF: docetaxel 75 mg/m² day 1, cisplatin 100 mg/m² day 1, and 5-FU 1000 mg/m² by continuous infusion for 4 days; and PF: cisplatin 100 mg/m² day 1, and 5-FU 1000 mg/m² as a continuous infusion for 5 days) for 3 cycles as opposed to the 4 cycles in TAX 323. With a minimum follow-up of 2 years, the risk of death was reduced by 30% in patients who had received TPF compared with the PF group (HR 0.70, $P = .006$). Overall survival at 3 years was 62% in the TPF group and 48% with PF. Interestingly, the rate of locoregional recurrences with TPF

was significantly better than that with induction treatment with PF, whereas distant metastatic failures were only slightly and nonsignificantly reduced (5% vs. 9%, $P = .14$). It is worth noting, however, that the rate of distant metastases was remarkably low in both arms. Subgroup analysis of patients with hypopharyngeal ($n = 89$) and laryngeal ($n = 77$) primary revealed that with 41 months median follow-up, median overall survival was 59 (31–NR) vs. 24 (13–42) months, and the HR for mortality was 0.62 (0.41–0.94; $P = .02$); the median PFS was 21 (12–58) versus 11 (8–14) months and the HR was 0.66 (0.45–0.97; $P = .03$), for TPF and PF, respectively. Among 67 and 56 operable patients in the TPF and PF arms, respectively, laryngectomy-free survival was significantly greater with TPF; the HR was 0.59 (0.37–0.95; $P = .03$). The 3-year LFS was 52% (39%–65%) versus 32% (19%–45%) favoring TPF (22). With the results of previous phase III trials showing equivalence for laryngectomy-free survival and overall survival (OS) with PF or CRT,

TABLE 4.4
Survival results of TAX 324

	TPF-255	PF-246
Median Survival (Mo)	70.6+	30.1
95% CI	49–NR	20.9–51.5
Died	41%	53%
KAPLAN-MEIR SURVIVAL		
1-Year	80% [75.0–84.9]	69% [64.1–75.7]
2-Year	67% [61.5–73.2]	54% [48.2–60.8]
3-Year	62% [55.9–68.2]	48% [41.7–54.5]
HAZARD RATIO TPF:PF		
[95% CI]	0.70 [0.54–0.90]	
Log-Rank <i>P</i> value	.0058	

these results support the use of induction CT with TPF and carboplatin/CRT as another acceptable treatment option for organ preservation in laryngeal and hypopharyngeal cancer. As expected, TPF was associated with a higher rate of neutropenia and neutropenic fever than PF (83% vs. 56% and 12% vs. 7%), but there was no difference in the rate of documented neutropenic infections. In addition, there were significantly fewer dose delays in the TPF arm and fewer dose reductions, which were entirely due to prolonged neutropenia in the PF arm (39% vs. 1%; $P < .001$).

The French-based Groupe d'Oncologie-Radiothérapie de la tête et cou (GORTEC) study 2000–2001 was designed to determine if the addition of docetaxel to PF induction CT results in a higher rate of organ preservation in patients with operable locally advanced laryngeal and hypopharyngeal cancer (23). Treatment-naïve patients were randomized to receive 3 cycles of PF or TPF. Responding patients with tumor regression more than 50% and recovery of normal laryngeal mobility then received 70 Gy RT. The major end point of this trial, as with the EORTC 24954 study, was functional larynx preservation, which was

defined as patients who are alive with an intact larynx without tracheostomy, tracheotomy, or gastrostomy. As of this time, the results of this study have been presented as an abstract only. The overall response rate was significantly higher in the TPF arm (82.8% vs. 60.8%; $P = .0013$), and a statistically significant increase in the number of patients proceeding to laryngeal preserving treatment was observed (80% vs. 58%). Total laryngectomy was performed on fewer patients in the TPF arm (16% vs. 32%). Overall, functional laryngeal preservation was 63% in the TPF arm and 41% in the PF arm ($P = .03$).

Recently, data from an interim analysis of an ongoing Italian study were presented in abstract form. In this trial, 101 patients with locally advanced stage III–IV were randomized so far to CRT using 2 cycles of cisplatin 20 mg/m² days 1 to 4 and 5-FU 800 mg/m² as a 96-hour confidence interval (CI) weeks 1 and 6 during RT (66–70 Gy) (Arm A) or TPF induction CT for 3 cycles (docetaxel 75 mg/m² and P 80 mg/m² on day 1, F 800 mg/m² 96 hours CI) every 3 weeks followed by the same CT/RT (Arm B). Radiological evaluation of responses 6 to 8 weeks from the end of CT/RT showed a complete response (CR) of 21.2% (CI, 64–89) in arm A and 50.0% (CI, 34–65) in arm B. Radiological CRs at 8 months for unresected patients were 40.0% in Arm A and 57.1% in Arm B. A trend toward superior survival was observed with the median OS, and 1-year OS were respectively 33.3 months and 77.6% in Arm A, whereas median OS was not reached in arm B and 1-year OS was 86.0% (24).

Recently, results of a randomized phase III trial conducted in Spain comparing TPF followed by chemoradiation with cisplatin were presented. In this study, 439 patients were evaluated. Despite methodological problems, patients who received induction CT had significantly longer time to failure (12.5 vs. 4.9 months; $P < .001$) and superior locoregional control (60.9% vs. 44.5%) compared with CRT alone. However, grade 3 and 4 toxicities including febrile neutropenia and mucositis were more frequent in the induction CT treatment arm (25).

Another randomized phase III trial (PARADIGM) based in the United States comparing induction with TPF to CRT alone is closed to accrual and the data are currently maturing.

■ OTHER INDUCTION CHEMOTHERAPY REGIMENS

The arrival of targeted agents has expanded treatment options in patients with SCCHN in recent years. Because of their distinct mechanism of action and therefore different side effect profiles, new combination regimens with acceptable toxicity profiles have become available. Especially the epidermal growth factor receptor (EGF-R) antagonists have been tested extensively since the late 1990s in patients with HNSCC. Emerging data suggest that the combination of the monoclonal antibody cetuximab (Erbix) with platinum plus 5-FU is safe and results in a survival advantage in patients with incurable head and neck cancer (26). After induction PCC, nine patients (19%) achieved a complete response, and 36 patients (77%) achieved a partial response. The most common grade 3 or 4 toxicity was skin rash (45%), followed by neutropenia (21%) without fever. At a median follow-up time of 33 months, locoregional or systemic disease progression was observed in six patients. The 3-year progression-free survival (PFS) and overall survival (OS) rates were 87% (95% CI, 78% to 97%) and 91% (95% CI, 84% to 99%), respectively (27). The Eastern Cooperative Group is currently testing a similar regimen using induction therapy with cetuximab, weekly carboplatin, and paclitaxel followed by combined CRT with weekly cetuximab, carboplatin, and paclitaxel plus RT (28). Preliminary data suggest a high number of complete responses at the end of induction and after completion of chemoradiation. Survival data—the primary end point—is maturing at this point. Recently, results from a phase I trial with TPF plus cetuximab were published, suggesting that the combination is safe with a lower 5-FU dose (850 mg/m²) to reduce GI toxicity (29). In this trial, all patients achieved at least a partial response, and 22 out of

28 patients had a radiographic complete response. With a median follow-up of 8 months, 85% of patients remained without evidence of disease, and 4 failures were observed (15%).

■ SUMMARY AND OUTLOOK

After 3 decades of clinical trials, CT is an established part in the treatment of patients with locally advanced SCCHN. In patients who are candidates for induction CT, TPF is now the new standard of care on the basis of 3 studies positive for improved survival or organ preservation as well as reduced toxicity with TPF compared with PF. TPF induction therapy can be safely delivered with the appropriate supportive measures. Patient selection is crucial, and close monitoring is important. It is also imperative that RT is not delayed after induction therapy. Early involvement of the radiation oncologist is crucial to assure a smooth and rapid transition from induction to RT or CRT. Most investigators using TPF in trials have abandoned radiation without concomitant CT after induction TPF and have adopted CRT in the sequential therapy approach as it is used in Tax 324. Weekly therapy with carboplatin as a radiation sensitizer is supported by a randomized trial in nasopharynx cancer, which proved equivalent efficacy and significantly less toxicity compared with bolus cisplatin (30). Finally, randomized trials demonstrate that PF is equivalent to CRT for survival or organ preservation. If TPF is significantly better than PF, then it is possible but definitely not proven that TPF is better than CRT alone with cisplatin. Currently, trials are under way to explore whether TPF induction CT can improve outcomes compared with standard CRT alone, and results are eagerly awaited. While these trials are ongoing we can recommend that TPF sequential therapy and CRT may both be considered acceptable regimens for treatment of patients with locally advanced disease. Given the excellent efficacy and good tolerability of this regimen, the activity of TPF may be further enhanced by the addition of targeted therapies, and currently ongoing phase I and II studies are addressing this question.

■ REFERENCES

1. Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. *CA Cancer J Clin.* 2007; 57:43–66.
2. Seiwert TY, Cohen EE. State-of-the-art management of locally advanced head and neck cancer. *Br J Cancer.* 2005;92:1341–1348.
3. Pignon JP, Bourhis J, Domenge C, Designe L. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. *Lancet.* 2000;355:949–955.
4. Monnerat C, Faivre S, Temam S, Bourhis J, Raymond E. End points for new agents in induction chemotherapy for locally advanced head and neck cancers. *Ann Oncol.* 2002;13:995–1006.
5. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. The Department of Veterans Affairs Laryngeal Cancer Study Group. *N Engl J Med.* 1991;324:1685–1690.
6. Lefebvre JL, Chevalier D, Lubinski B, Kirkpatrick A, Collette L, Sahmoud T. Larynx preservation in pyriform sinus cancer: preliminary results of a European Organization for Research and Treatment of Cancer phase III trial. EORTC Head and Neck Cancer Cooperative Group. *J Natl Cancer Inst.* 1996;88:890–899.
7. Forastiere AA, Goepfert H, Maor M, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *N Engl J Med.* 2003;349:2091–2098.
8. Zorat PL, Paccagnella A, Cavaniglia G, et al. Randomized phase III trial of neoadjuvant chemotherapy in head and neck cancer: 10-year follow-up. *J Natl Cancer Inst.* 2004;96:1714–1717.
9. Paccagnella A, Orlando A, Marchiori C, et al. Phase III trial of initial chemotherapy in stage III or IV head and neck cancers: a study by the Gruppo di Studio sui Tumori della Testa e del Collo. *J Natl Cancer Inst.* 1994;86:265–272.
10. Al-Sarraf M, LeBlanc M, Giri PG, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. *J Clin Oncol.* 1998;16:1310–1317.
11. Denis F, Garaud P, Bardet E, et al. Final results of the 94-01 French Head and Neck Oncology and Radiotherapy Group randomized trial comparing radiotherapy alone with concomitant radiochemotherapy in advanced-stage oropharynx carcinoma. *J Clin Oncol.* 2004;22:69–76.
12. Calais G, Alfonsi M, Bardet E, et al. Randomized trial of radiation therapy versus concomitant chemotherapy and radiation therapy for advanced-stage oropharynx carcinoma. *J Natl Cancer Inst.* 1999;91:2081–2086.
13. Jeremic B, Shibamoto Y, Milicic B, et al. Elective ipsilateral neck irradiation of patients with locally advanced maxillary sinus carcinoma. *Cancer.* 2000;88:2246–2251.
14. Vermorken JB. Medical treatment in head and neck cancer. *Ann Oncol.* 2005;16(suppl 2):ii258–ii264.
15. Domenge C, Hill C, Lefebvre JL, et al. Randomized trial of neoadjuvant chemotherapy in oropharyngeal carcinoma. French Groupe d'Etude des Tumeurs de la Tete et du Cou (GETTEC). *Br J Cancer.* 2000; 83:1594–1598.
16. Lefebvre J, Horiot J, Rolland F, et al. Phase III study on larynx preservation comparing induction chemotherapy and radiotherapy versus alternating chemoradiotherapy in resectable hypopharynx and larynx cancers. EORTC protocol 24954–22950. Proceedings of the American Society of Clinical Oncology [Abstract LBA6016]. 2007;25.
17. Haddad R, Colevas AD, Tishler R, et al. Docetaxel, cisplatin, and 5-fluorouracil-based induction chemotherapy in patients with locally advanced squamous cell carcinoma of the head and neck: the Dana Farber Cancer Institute experience. *Cancer.* 2003; 97:412–418.
18. Haddad R, Tishler R, Wirth L, et al. Rate of pathologic complete responses to docetaxel, cisplatin, and fluorouracil induction chemotherapy in patients with squamous cell carcinoma of the head and neck. *Arch Otolaryngol Head Neck Surg.* 2006;132:678–681.
19. Schrijvers D, Van Herpen C, Kerger J, et al. Docetaxel, cisplatin and 5-fluorouracil in patients with locally advanced unresectable head and neck cancer: a phase I-II feasibility study. *Ann Oncol.* 2004;15:638–645.
20. Vermorken JB, Remenar E, van Herpen C, et al. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. *N Engl J Med.* 2007;357: 1695–1704.
21. Posner MR, Herschock DM, Blajman CR, et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. *N Engl J Med.* 2007;357:1705–1715.
22. Posner MR, Norris CM, Tishler R, Wirth L, Haddad R, Group TS. Sequential therapy for locally advanced larynx and hypopharynx cancer: Subgroup analysis

- from the TAX 324 Study. Proceedings of the American Society of Clinical Oncology [Abstract 6031]. 2008;26.
23. Pointreau Y, Garaud P, Chapet S, Sire C, Tuchais C, Tortochaux J, et al. Randomized Trial of Induction Chemotherapy With Cisplatin and 5-Fluorouracil With or Without Docetaxel for Larynx Preservation. *J Natl Cancer Inst*. 2009 April 1; 2009;101(7):498–506.
 24. Paccagnella A, Ghi MG, Loreggian L, Buffoli A, Koussis H, Mione CA, et al. Concomitant chemoradiotherapy versus induction docetaxel, cisplatin and 5 fluorouracil (TPF) followed by concomitant chemoradiotherapy in locally advanced head and neck cancer: a phase II randomized study. *Ann Oncol*. 2009 Jul;21(7):1515–1522.
 25. Hitt R, Grau JJ, Lopez-Pousa A, et al. Final results of a randomized phase III trial comparing induction chemotherapy with cisplatin/5-FU or docetaxel/cisplatin/5-FU follow by chemoradiotherapy (CRT) versus CRT alone as first-line treatment of unresectable locally advanced head and neck cancer (LAHNC). Proceedings of the American Society of Clinical Oncology [Abstract 6009]. 2009.
 26. Vermorken JB, Mesia R, Vega V, et al. Cetuximab extends survival of patients with recurrent or metastatic SCCHN when added to first line platinum based therapy—Results of a randomized phase III (Extreme) study. Proceedings of the American Society of Clinical Oncology [Abstract 6091] 2007.
 27. Kies MS, Holsinger FC, Lee JJ, William WN, Jr., Glisson BS, Lin HY, et al. Induction chemotherapy and cetuximab for locally advanced squamous cell carcinoma of the head and neck: results from a phase II prospective trial. *J Clin Oncol*. 2009 Jan 1;28(1):8–14.
 28. Wanebo HJ, Ghebremichael M, Burtress B, et al. Phase II evaluation of cetuximab (C225) combined with induction paclitaxel and carboplatin followed by C225, paclitaxel, carboplatin, and radiation for stage III/IV operable squamous cancer of the head and neck (ECOG, E2303). Proceedings of the American Society of Clinical Oncology [Abstract 6015]. 2007;25.
 29. Haddad RI, Tishler RB, Norris C, et al. Phase I study of C-TPF in patients with locally advanced squamous cell carcinoma of the head and neck. *J Clin Oncol*. 2009;27:4448–4453.
 30. Chitapanarux I, Lorvidhaya V, Kamnerdsupaphon P, et al. Chemoradiation comparing cisplatin versus carboplatin in locally advanced nasopharyngeal cancer: randomised, non-inferiority, open trial. *Eur J Cancer*. 2007;43:1399–1406.

CHAPTER 5

Endoscopic Head and Neck Surgery: The Impact of Minimally Invasive Surgery Within Multidisciplinary Care

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■ INTRODUCTION

Minimally invasive approaches and endoscopic head and neck surgery (eHNS) represent a great leap forward for patients with tumors of this region and for future of multidisciplinary care in head and neck oncology. For cancers of the upper aerodigestive tract, eHNS has developed around a foundation in transoral resection techniques whereby tumors are removed through the natural orifice of the mouth. For tumors of the neck and thyroid, eHNS techniques have been developed that allow excision of lesions via small inconspicuous incisions located some distance from the primary tumor site. Furthermore, minimally invasive endoscopic surgical techniques can obviate the need for extensive open or craniofacial approaches for tumors of the skull base and paranasal sinuses. Terms such as natural orifice transluminal endoscopic surgery, transoral robotic surgery (TORS), endoscopic laser surgery (ELS), transoral laser microsurgery (TLM), and robotic thyroidectomy have all gained in popularity over the years and are part of the growing armamentarium within the field of eHNS.

Proponents of eHNS techniques point to a significant reduction in trauma to uninvolved structures that often accompanies conventional ablative surgery. Preservation of tissue planes and small wounds, it is reasoned, lead to conservation of anatomical and physiological function. Furthermore, patients experience less pain and fewer complications and recover earlier than following conventional open surgery often with superior aesthetic and functional results. In addition, the use of eHNS does not preclude any further therapeutic regimens should the patient require postoperative adjuvant therapy and experience recurrent or second primary disease. eHNS is, however, not without potential limitations. Disadvantages include the rejection of some long held and traditional surgical beliefs and also new discomforts associated with limited direct access and reliance sometimes on endoscopic 2-dimensional visualization. Indeed in many cases, the surgeons may no longer directly visualize or handle the tissues they are operating on. The financial start-up costs of instrument and equipment purchase, personnel and training, as well as the expenses associated with initiating,

maintaining, and evolving costly technologies can be prohibitive for some institutions.

Endoscopic Laser Surgery and Transoral Laser Microsurgery

First devised by Strong and Jako in 1972 and developed by Steiner and others, ELS and TLM have emerged as a standard of care for early laryngeal cancer and also an attractive treatment alternative for select tumors of the oropharynx, supraglottis, and hypopharynx (1–7). ELS has developed along traditional Halsteadian oncologic principles with excision of the tumor in a circumferential, en-bloc manner (8–10). In TLM, the surgeon divides the tumor repeatedly under the operating microscope to assess the extent and depth of invasion and to facilitate a more “logical” minimal resection (11). By conserving the maximum amount of unaffected tissues, structure and function are both preserved. Both methods have their proponents, but what is

common to each is an approach that avoids the often debilitating sequelae that can follow chemoradiotherapy or open laryngeal surgery.

Endoscopic Laser Technology and Equipment

TLM and ELS are endoscopic surgical techniques performed under direct laryngoscopy, with suspension/fixation and the use of an operating microscope (Figure 5.1) (12), microsurgical instruments (Figure 5.2), and carbon dioxide (CO₂) laser. It is an adaptive surgical technique, relying on the surgeon’s understanding of the 3-dimensional anatomy of the tumor’s extent and surrounding anatomy.

Fundamental to the continued benefit of eHNS are new technologies that allow exceptional visualization and permit precise tissue instrumentation through narrow or restrictive access points. For some cases, direct line-of-sight visibility may at times be impossible, and with it, line-of-sight

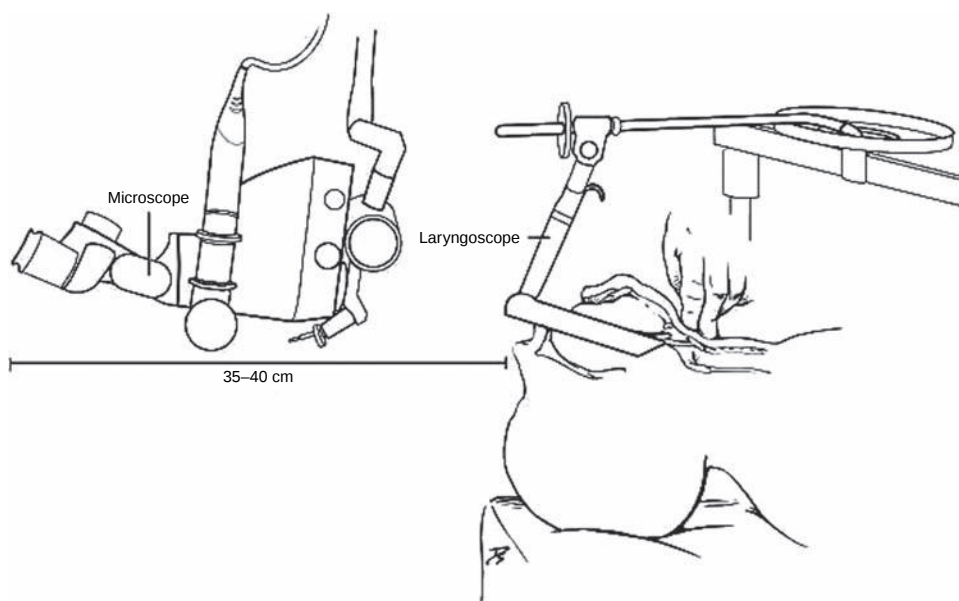


FIGURE 5.1

The technique of direct laryngoscopy and the use of an operating microscope to visualize the laryngopharynx for endoscopic resection. Reprinted with permission from Ref. 12.

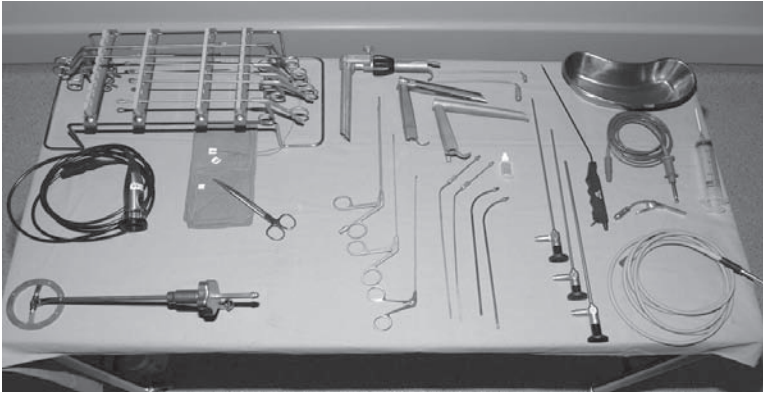


FIGURE 5.2

The intraoperative table containing endoscopes and the microsurgical equipment required for transoral laser microsurgery.

cutting instruments such as the free-beam laser are of limited use. With its power and absorption characteristics, the carbon dioxide (CO_2) laser remains among the most useful cutting device for operation in the aerodigestive tract. Its long wavelength (10 600 nm) and physical properties have until recently mandated deploying the laser beam in a direct path from a microscope mounted mirror manipulator to the end organ. The line of site restriction limits the “workspace” of the laser within which the surgeon can work and proves problematic as tumor size increases or patient anatomy restricts line-of-sight delivery. The Omni Guide System (Omni Guide, Inc., Cambridge, Massachusetts),

has been developed to deliver a CO_2 laser via a flexible hollow core fiber (13–14). The system allows delivery of CO_2 laser energy to areas of the head and neck in which the direct visualization required for conventional linear CO_2 laser systems cannot be acquired. The flexibility of the fiber delivery system permits either handheld operation or alternatively the fiber can be mounted to a specialized robotic manipulator to facilitate cutting at increased angles thus increasing the potential work space at the tumor patient (Figure 5.3).

Other fiber-based laser technologies are beginning to find uses for the treatment of head and neck cancer. Thulium-ion-based continuous

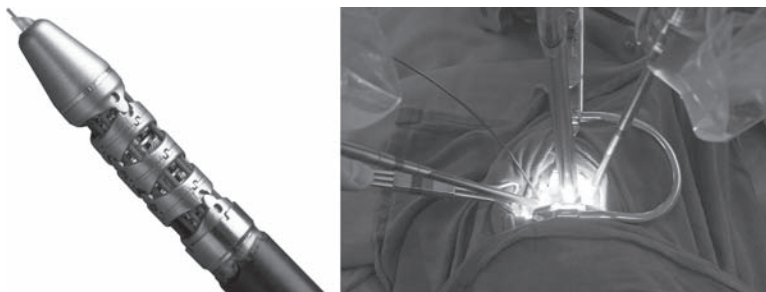


FIGURE 5.3

On the left panel, the robotic instrument with a mounted laser fiber is shown. On the right, the laser connected to the robotic instrument is being used in TORS.

wave lasers have similar properties to CO₂ lasers and demonstrate promise for benign laryngeal and tracheal disease, as well as, for cancer (15–16). The 2013 nm wavelength of this laser allows its energy to be delivered by a small caliber glass fiber, yet it retains water as a chromophore. This laser therefore offers a smooth vaporization pattern and excellent hemostasis, similar to that realized with the potassium titanyl phosphate laser but with less risk of deep tissue penetration, as it has an absorption length of only 0.180 nm (17). The acquisition of a variety of specialized endoscopes and endoscopic instruments is an important consideration in developing an ELS or TLM practice; these include a selection of graspers, manipulators, diathermy and suction devices, and endoscopic hemostatic clip applicators.

eHNS and Early Laryngeal Cancer

In 2002, a review by the Cochrane Collaboration was performed examining the evidence base for the treatment of laryngeal cancer with conventional open laryngeal surgery versus radiotherapy versus endoscopic surgery (with or without laser) in T1 and T2 laryngeal cancer (18). Only 1 randomized control trial was found investigating the relationship of surgery versus radiotherapy for early glottic cancer (19). The multicenter randomized controlled trial published in 1990 from Eastern Europe, recruited patients to open surgery, radiotherapy or a combination of radiotherapy and chemotherapy but crucially did not include endolaryngeal surgery. The Cochrane review concluded that the methodology of the study was insufficiently robust to draw any significant conclusions from the data presented.

To resolve the management conflicts of early laryngeal cancer, 2 large multicenter randomized controlled trials comparing radiotherapy to ELS and TLM for early glottic cancer were devised by Coman in Brisbane, Australia and by Birchall in Bristol, United Kingdom. Unfortunately as a result of problems relating to patient recruitment and ethical concerns by participating institutions

surrounding treatment equipoise, both trials had to be abandoned (20–21).

With the prospects of completing a level 1 randomized control trial remaining somewhat remote, attention must turn to the available evidence base reported in the literature. A search of Medline or PubMed will reveal several hundred case series studies and a handful of nonrandomized comparative cohort studies reporting the oncologic effectiveness of TLM or ELS in the treatment of laryngeal cancer. eHNS is an effective oncologic treatment at the primary tumor site. Local control rates for eHNS in the treatment of early laryngeal cancer have been reported at between 85% and 96% for T1 tumors, and 66% to 100% for T2 lesions (22–29).

eHNS & Laryngeal Cancer: Quality of Life (QOL) and Voice

There have been several retrospective cohort studies and 3 nonrandomized comparative studies evaluating QOL, swallowing, and voice following radiotherapy or eHNS for early glottic cancer (30–32). Overall, none of the studies demonstrated a significant difference between outcomes following either eHNS or radiotherapy; however, some interesting details emerge if the studies are examined more closely. Stoeckli et al examined a retrospective cohort of patients with T1 and T2 laryngeal cancers treated with either radiotherapy or eHNS using the EORTC (European Organization for Research and Treatment of Cancer) QOL questionnaire (QLQ-C30 and H&N 35) with 90% compliance rate in 62 patients ($n = 56$) (30). Overall, the authors found no significant differences between surgery and radiation in global QOL, but within specific head and neck QOL, swallowing, dry mouth, and dental problems were, as expected, worse in the radiotherapy group. A retrospective cohort study with a 55% response rate by Smith et al using the UW-QOL-R (Revised University of Washington Quality of Life questionnaire) and the PSS-HN (Performance Status Scale for Head and Neck) demonstrated no significant difference

between patients with Tis and T1 glottic cancer treated with radiotherapy versus those treated with endoscopic surgery (31).

Loughran et al studied 36 patients with Tis and T1 glottic cancer treated with either endoscopic resection or radiation. The full armamentarium of validated outcome measures was used including UW-QOL; VHI (Voice Handicap Index); Vocal performance Questionnaire; VoiSS (Voice Symptom Scale); expert rating of Grade, Roughness, Breathiness, Asthenia, and Strain; and Functional Assessment of Cancer Therapy head and neck questionnaire. The authors concluded that no significant difference existed between endoscopic surgery and radiotherapy in self-reported or expert-rated scores except that in the VoiSS emotional impact outcome, which was less for radiation (32).

In 2006, Cohen et al performed meta-analysis comparing posttreatment voice outcomes using the VHI between radiotherapy and TLM. Six studies with 208 patients were identified that directly compared the VHI between patients receiving radiotherapy or ELS. The analysis demonstrated that voice outcomes were similar ($P = .1$) after either radiotherapy or TLM (33). This study debunks a long-held belief that voice outcomes are superior in patients treated with radiation therapy.

eHNS: Advanced Laryngeal Cancer

Despite several randomized prospective trials comparing radiation therapy with or without chemotherapy to surgery, no single approach has had a significant impact on overall survival for the treatment of advanced stage head and neck cancer. Thus, a strong emphasis on functional results as an indicator of treatment success has evolved. In some centers in Europe and North America, TLM has been advocated as an effective organ-sparing approach for select advanced laryngeal cancer. A combined multicenter study of 117 patients undergoing TLM with or without adjuvant radiotherapy for stage III and IV laryngeal cancer demonstrated 2- and 5-year local disease control

rates of 82% and 74%, respectively (34). Only 15/117 patients (13%) in the cohort required adjuvant radiotherapy to the primary tumor site. In the subgroup of patients treated in North America, the average length of stay in hospital after surgery was only 5.7 days (median 5 days, range 1–16 days). In terms of functional outcomes, 68/117 patients were alive with no evidence of disease recurrence and a preserved larynx at their last follow-up. As a primary surgical approach, TLM achieved a 2-year actual laryngeal preservation rate of 92% (83/90). Two of 68 patients (3%) were tracheotomy dependent and 5 of 68 patients (7%) were feeding tube dependant. It was concluded that TLM offers acceptable oncologic and functional results, with most patients receiving single modality therapy with the added benefit of shortened periods of hospitalization.

eHNS and Oropharyngeal Cancer

The role of eHNS techniques in the management of oropharyngeal cancer remains controversial. The emerging influence of HPV-associated oropharyngeal cancer has further complicated optimum treatment selection (35). Many institutions now favor up front primary radiotherapy with or without chemotherapy given the comparable outcomes for surgery and radiotherapy (36). Critics of surgical techniques such as TLM point out that as many cases are followed by adjuvant radiotherapy to the neck and primary site, the rationale for using surgery is unclear. In a study of 69 patients with select T1-T3, N0-N2 oropharyngeal cancers treated with TLM surgery alone without adjuvant radiotherapy to the primary or neck local control was achieved in 66/69 patients (37). Furthermore, locoregional control for all patients was 84%, with all patients who developed regional recurrence successfully salvaged with surgery or radiotherapy.

TLM has considerable advantages over radiotherapy or concurrent chemoradiotherapy including lower morbidity, short duration of treatment, and patient acceptability. TLM reestablishes the

principle of surgery first (as in the open surgery first era) to render local and regional disease control and more accurately identify the requirement for and extent of any adjuvant therapy. Adverse function in patients with oropharyngeal cancer has been shown to be correlated with the use of radiotherapy (38).

Indeed, the published experiences with TLM suggest a greater role for surgery first, not only to render local and regional disease control but also to more accurately identify the requirement for and extent of any adjuvant therapy. TLM has considerable advantages over radiotherapy or concurrent chemoradiotherapy including lower morbidity, short duration of treatment, and patient acceptability. TLM may be preferable for patients not only because of its low morbidity and mortality but also because they can return quickly to their normal routine. Perhaps for properly selected patients, RT or eHNS is equally effective. Yet, without a national cooperative group to study surgery, a randomized prospective trial seems unlikely. Nonetheless, as head and neck surgeons, we urge that such a prospective trial be performed through the existing NIH-sponsored intergroup framework.

In the meantime, we argue that it is the changing epidemiology of oropharyngeal cancer that will lead to a greater role for eHNS in the management of this disease. Several reports from the United States and abroad have documented the precipitous rise in the incidence of OPSCC in individuals younger than 40 years (39). These TLM experiences suggest a greater role for surgery first, not only to render local and regional disease control but also to more accurately identify the requirement for and extent of any adjuvant therapy. TLM has considerable advantages over radiotherapy or concurrent chemoradiotherapy including lower morbidity, short duration of treatment, and patient acceptability. TLM may be preferred by patients not only because of its low morbidity and mortality but also because patients can return quickly to their normal routine.

It is likely that the changing epidemiology of oropharyngeal cancer and younger age at diagnosis will lead to a greater role for eHNS in the

management of this disease. Molecular epidemiologic evidence suggests an association between human papillomavirus (HPV) and OPSCC (39). Different reports have demonstrated the presence of HPV DNA in at least 50% of oropharyngeal squamous cell carcinomas. Moreover, patients who are seropositive for HPV subtype 16 have a 7-fold increased risk of developing a squamous cell cancer positive for HPV 16 DNA as compared to their seronegative counterparts (40). Chaturvedi et al and others have attributed the increase in incidence of HPV-related oral and OPSCCs in the United States between 1973 and 2004 to changing sexual habits (41). A genetic susceptibility to a latent chronic HPV infection is probably necessary for the development of HPV+ head and neck cancer, though no genetic marker (such as a single nucleotide polymorphism) has yet been identified; the International Head and Neck Cancer Epidemiology consortium has identified this as an important research objective.

As these issues are addressed in the laboratory and in cooperative group trials, we believe that now is the time to revisit our basic assumptions about a radiation-based approach. In fact, one compelling argument is that, given the potential long-term sequelae (42) of radiation for a younger population (43), eHNS must play a greater role in the management of patients with oropharyngeal cancer. Since HPV-associated oropharyngeal cancers have a more favorable outcome, when compared with non-HPV-associated tumors, this finding is even more compelling rationale for the prospective multicenter evaluation of techniques in eHNS.

Robotic Head and Neck Surgery

Czech writer Josef Čapek introduced the term “robot” to his brother Karel Čapek, a fellow playwright, who used the expression to describe several characters in his stage play “R.U.R. (Rossum’s Universal Robots)”. More widely appreciated is the term “robotics” and the famous “three laws of robotics” created by the science-fiction writer

Isaac Asimov. Although these literary aspects of robotics are relatively straightforward, a precise technical definition of what a robot actually is remains somewhat more difficult to describe. The Society of American Gastrointestinal and Endoscopic Surgeons and the Minimally Invasive Robotic Association defined as part of a consensus document in 2007 robotic surgery as “a surgical procedure or technology that adds a computer technology-enhanced device to the interaction between a surgeon and a patient during a surgical operation and assumes some degree of control heretofore completely reserved for the surgeon” (44).

For head and neck surgery, natural access through both the mouth and axilla provides ample opportunity for innovation and improvement of current endoscopic and minimally invasive techniques. Accordingly, several exciting and novel applications are emerging for eHNS in the last decade. In 2003, the first head and neck robotic surgery was performed at the Walter Reed Army Medical Center, with the resection of a symptomatic vallecular cyst (45). McLeod and Melder delivered 8-mm robotic arms using a “standard” da Vinci Surgical System (Intuitive Surgical Inc., Sunnyvale, CA) through a slotted laryngoscope in a brief procedure but did not use multiple robotic arms.

Robotic Equipment and Technology

Currently, the only platform for head and neck robotic surgery is the da Vinci Surgical System (Intuitive Surgical Inc., Sunnyvale, CA.). The da Vinci Surgical Robotic System uses teleoperators and is controlled by a surgeon sitting at a remote console, in a “master-slave” configuration (Figure 5.4). The surgeon is provided with an endoscopically derived 3-dimensional visual display that is collocated with control handles that direct movements of the robot’s instruments inside the patient’s body.

The da Vinci robot has been used for a number of types of minimally invasive surgery including cardiac, abdominal, and urology techniques. The principal advantages of endoscopic robotic surgery include increased visualization, enhanced manipulation of tissues, and the elimination of line of

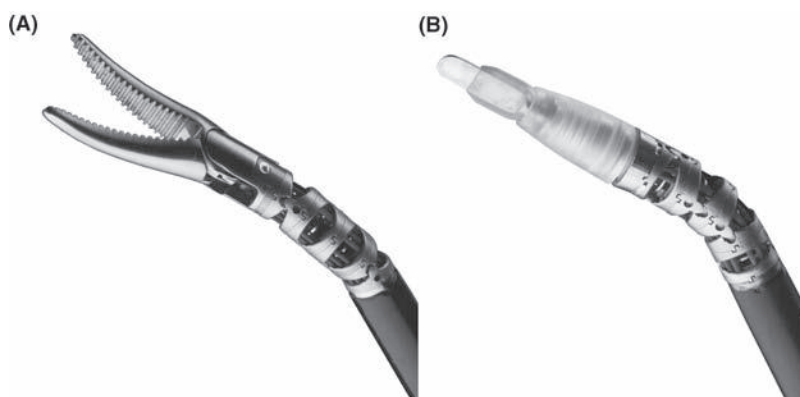


FIGURE 5.4

A surgeon at work at the remote console using “master-manipulators,” which directly control movements on the surgical instruments placed within the surgical site within the patient’s body.

site restrictions thus increasing the workspace at the operative site. Furthermore, proponents of robotic surgery point to its minimal invasiveness, decreased pain, faster recovery, and lower morbidity when compared with equivalent open surgical procedures. Furthermore, motion scaling increases precision and reduces the larger hand movements required by humans while eliminating tremor and fatigue.

For robotic head and neck surgery, 3 of the 4 da Vinci robotic arms are used. After placing a suitable oral retractor, such as the Fehr-Kastenbauer endoscope, Crowe-Davis, or Dingman oropharyngoscope, the endoscope or camera is introduced into the pharynx followed by 2 other arms carrying interchangeable 5-mm-wide working instruments, including the Maryland grasping forceps and the “spatula tip” electrocautery (Figure 5.5). Interestingly the TORS setup still relies heavily on the presence of a human assistant to sit at the patient’s side and provides assistance with precisely targeted suction and retraction. A variety of manipulators and dissectors can be used during surgery. The cutting instruments are either an electrocautery tool or cold steel dissector, although, as mentioned earlier, a laser instrument will soon be available. The recent adaptation of robot manipulators for the deployment of laser cutting technology has

**FIGURE 5.5**

(A) 5-mm Maryland dissecting forceps. (B) A 5-mm rounded "spatula" tip used for electrocautery.

proved a popular addition to the eHNS armamentarium (46). Although the Bovie cutting diathermy is an effective instrument, some eHNS operators prefer the precision, nominal thermal damage, and reduced tissues necrosis offered by fiber laser technologies such as the carbon dioxide and Thulium laser (46,47).

Although robotic head and neck surgery and TLM are complimentary, they are 2 very different surgical techniques. With TLM, the dissection proceeds at the microsurgical level with the aid of high magnification allowing careful evaluation of the tumor host interface. TLM can be used for tumors of the entire upper aerodigestive tract, while Robotic head and neck surgery is optimally suited for tumors of the oropharynx as well as selected lesions of the supraglottic larynx and hypopharynx. The body of literature supporting the evidence base for robotic head and neck surgery remains in its infancy (48).

The University of Pennsylvania is the first to systemically study robotic head and neck surgery. Hockstein et al first studied the feasibility of robotics in mannequin, animal, and cadaveric models using the da Vinci surgical robot (49–55), moving away from laryngoscopes and using wide oral and oropharyngeal exposure. From these laboratory studies to the first case series on human subjects, investigators from the University of Pennsylvania

have lead the way in the initial development of TORS for oropharyngeal and supraglottic tumors (56–58). Other authors have reported success with the da Vinci platform with applications in the pediatric airway (59), nasopharynx (60), and skull base (61).

As with any new surgical technology, intraoperative safety is a critical issue. Initial experiments performing TORS with the da Vinci Surgical System on human cadavers has demonstrated that even with willful intention it is difficult if not impossible to inflict no more than superficial lacerations (62).

Endoscopic Approaches to the Thyroid and Neck

Endoscopic surgery of the neck can trace its origins to the first endoscopic parathyroidectomy performed in Cleveland on November 28, 1995 (63). Gagner used 5-mm laparoscopic instruments, a 30-degree endoscope, and continuous carbon dioxide gas insufflation at 15 mmHg to create a working space between the strap muscles and thyroid bed to identify and successfully remove a parathyroid adenoma. A year later, on July 8, 1996, Hüscher working in Italy performed the first endoscopic thyroid lobectomy

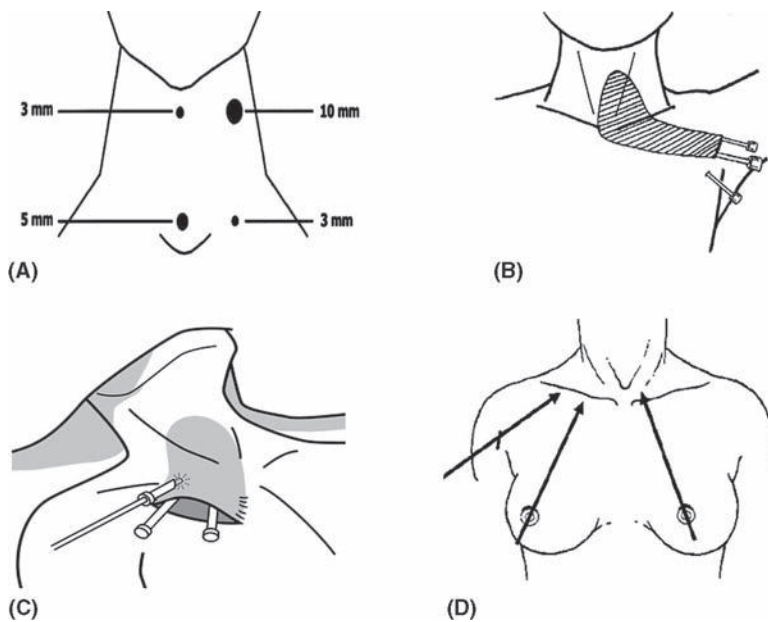


FIGURE 5.6

(A) The schema and incision sites for ports used in transcervical endoscopic approach for thyroidectomy, as pioneered by Inabnet and Gagner. (B) The “anterior chest-wall” approach for endoscopic thyroidectomy. (C) Ikeda and Takami’s schema for endoscopic thyroidectomy via axillary incisions and using insufflation. (D) Schema for the axillo-bilateral-breast approach or “ABBA” approach for endoscopic thyroidectomy.

using “low-pressure” carbon dioxide insufflation and a laparoscopic “wall-lifter” (Laparo Tenser, CHIO-MED Treviglio, Bergamo, Italy) (64).

Following these initial experiences, a variety of endoscopic approaches for the thyroid gland have evolved (65–69) and can be categorized as cervical versus extracervical approaches and then further classified based on the use of insufflation or not, the type of access to the thyroid bed (direct or indirect), and whether the robotic surgical system is used.

Inabnet and Gagner (70) described a series of 35 patients operated via an endoscopic, insufflating, and transcervical approach, with indirect access to the thyroid bed via 4 small laterally based incisions (Figure 5.6A) in 1997. Micolli reported success using a video-assisted direct endoscopic approach using a “mini-incision” for parathyroid adenomas (71) and in 1999 for thyroid lobectomy.

In Asia, Ishii et al first proposed and performed extracervical approaches for endoscopic thyroidectomy, presenting their work in 1998 in Rome, first using an “anterior chest-wall” approach (Figure 5.6B) and later using a “scarless” breast approach (68).

However, Ikeda and Takami were the first to describe in 1999 to 2000 the feasibility of endoscopic thyroidectomy via a camouflaged axillary incision (Figure 5.6C) (72). Carbon dioxide insufflation at 4 mmHg was used to maintain this “working space.” By placing the patient’s arm above the head and thus rotating the clavicle superomedially, the distance between neck and axilla was significantly diminished and excellent exposure could be obtained. Other groups have since described the “ABBA” or axillo-bilateral-breast approach (Figure 5.6D) (73–75). But many groups from Asia have focused on endoscopic thyroidectomy, via an axillary approaches (65,66,76–78). Among these are a large series of

patients from Seoul, Korea that have undergone robotic thyroidectomy incorporating the da Vinci Surgical System (79).

From the surgeon's perspective, this fusion of minimally invasive thyroid surgery techniques with the da Vinci Surgical System provides several distinct advantages. The 3-dimensional environment created with 30-degree capable endoscopy improves operative field visualization, and 540-degree enabled wristed instrumentation facilitates operative dexterity. The conventional open thyroidectomy approach however remains safe, effective, and time-honored and for this reason, many remain skeptical of robot-assisted techniques. The same skepticism accompanied the introduction of robotic-assisted prostatectomy when initially introduced in the United States. Currently around 70% of radical prostatectomies are now performed using the da Vinci Surgical System.

Robotic Thyroidectomy: Technique

In 2010, the first case report in North America using Chung's technique of robotic thyroidectomy was published (80). To illustrate the feasibility of this approach, the technique is briefly described below. The patient is positioned supine on a shoulder roll and the ipsilateral arm is extended cephalad to expose the axilla. First, a vertical line is marked in the midline from the sternal notch to the hyoid bone. Next, a 5- to 6-cm line is drawn along the lateral border of the pectoralis major muscle in the axilla. The arm is then placed into its natural position to confirm that the incision will be hidden postoperatively.

An incision is made along the line marked in the axilla allowing the skin, subcutaneous tissue, and platysma to be elevated off the pectoralis major muscle thus creating the "working space." Lighted breast retractors or a headlight is used to continue the dissection over the clavicle within the limits of the superficial skin markings made earlier. Next, the space between the clavicular and sternal head of the sternocleidomastoid muscle is

identified and opened superiorly. Here the omohyoid is retracted superiorly and posterolaterally or divided, and the sternohyoid and sternothyroid strap muscles are elevated thus exposing the thyroid gland. The modified Chung thyroid retractor with table mount lift (Marina Medical, Sunrise, Florida) is placed under the strap muscles and secured to the table mount lift. The lift is used to ensure an adequate working space with ample visualization of the thyroid and should be at least 4 cm in height at the opening. An 8-mm paramedian vertical incision is then made on the chest wall. A tract is created using hemostats and then a blunt-tipped trocar is placed and tunneled into the working space. This trocar is used to place the third arm of the robot and the ProGrasp instrument. The da Vinci Surgical System is then moved to a position that is adjacent to the table and the arms are oriented to insert the instruments. A 30-degree down stereoscopic endoscope camera is placed in the centre and should be low outside of the wound and high inside the wound. Then a 5-mm Harmonic Curved Shears and a 5-mm Maryland Dissector are placed in the axillary ports. The Harmonic Curved Shears are placed in the position that would correspond with the surgeon's dominant hand. The instruments should enter high in the wound and be angled to a low position, so that they are under the camera. Finally, an 8 mm ProGrasp Forceps is placed in the port that enters through the chest incision and is used to retract the thyroid and other tissues.

The superior pole of ipsilateral thyroid lobe is retracted with the ProGrasp forceps and dissected from the cricothyroid muscle and other surrounding tissues. Next, the superior vascular pedicle is transected with the Harmonic Shears. The inferior aspect of the thyroid is also dissected from the trachea using the Harmonic Shears. The thyroid is then retracted medially and ventrally, away from the trachea and paratracheal groove using the ProGrasp forceps. In so doing, the recurrent laryngeal nerve and both parathyroids are identified and preserved. Some authors advocate removal of the contralateral thyroid lobe via a unilateral axillary

incision. However, it should be noted that exposure of the nerve in the contralateral paratracheal groove is limited.

Studies have shown that when compared to conventional thyroidectomy, endoscopic techniques may be associated with less postoperative pain, shorter hospital stays, and higher patient satisfaction with cosmesis, voice, and swallowing (81,82). Furthermore, no significant differences have been found with regard to perioperative complications, surgical trauma, or thyroid capsular disruption (83). Until recently, endoscopic thyroidectomy was limited to small to moderate thyroid nodules with fine-needle aspiration biopsies consistent with benign or papillary thyroid cancer pathology. Now with improved ultrasound technology and better access to sonographic imaging, many patients have tumors identified at earlier stages. Consequently, there has been a move toward minimally invasive approaches with expansion of indications for endoscopic thyroidectomy to include more low- and intermediate-risk thyroid cancers (84). Despite the many advantages of minimally invasive thyroid surgery there have been some reports about tumor seeding at the insertion sites of the instrument ports. One case report details recurrent thyroid disease in the endoscopic subcutaneous tunnel in a 25-year-old woman following a breast approach endoscopic thyroidectomy (85). Another study reports the soft tissue implantation of thyroid adenomatous hyperplasia following endoscopic thyroid surgery. The authors hypothesize that postoperative implantation resulted from rupture of thyroid capsule during the surgical procedure (86). Other etiologic factors have been proposed including CO₂ displacement of tumor cells during insufflation and leakage of gas along the trocars causing seeding of tumor cells at port sites (87).

Extracervical approaches to the neck and the technique of robotic thyroidectomy represent not only a revolutionary new approach to the thyroid, but also a stepping stone to more complex operations of the neck, including tracheoesophageal resection and reconstruction,

laryngeal framework surgery, and even endoscopic neck dissection.

Endoscopic/Robotic-Assisted Neck Dissection

As the radical neck dissection has progressively been replaced by functional and selective neck dissections without compromising the oncologic outcome the extent and morbidity of neck dissection has steadily decreased. Several authors have proposed minimally invasive endorobotic or endoscopic neck surgery and reported successful outcomes following submandibular gland resections, selective neck dissections, parotidectomy, and thymectomy in porcine and human cadaver models (54,88–91).

■ SUMMARY

Now as an established discipline, eHNS encompasses the surgical techniques of TLM, TORS, as well as endoscopic, video-assisted, and robotic surgery of the neck and thyroid. For tumors of the upper aerodigestive tract, the systematic use of eHNS may help to de-escalate the intensity of radiation-based therapy for patients, eliminating the need for radiation and/or chemotherapy for some patients, while reducing the RT dose in others. In fact, the incorporation of eHNS into multidisciplinary care represents a fundamental paradigm shift for head and neck oncology.

For tumors of the glottic larynx, TLM remains the gold standard. For supraglottic laryngeal, oropharyngeal, and hypopharyngeal tumors, as well as selected other lesions, both TLM and TORS can be used. In the neck, endoscopic and video-assisted techniques are now an important part of thyroid and parathyroid surgery. In the next 5 years, with robotic surgery and laser technology as a common platform, we foresee the development and widespread use of several new and innovative procedures for head and neck surgery, via transoral and transaxillary approaches (92).

■ REFERENCES

- Strong MS. Laser excision of carcinoma of the larynx. *Laryngoscope*. 1975;85:1286–1289.
- Steiner W. Experience in endoscopic laser surgery of malignant tumours of the upper aero-digestive tract. *Adv Otorhinolaryngol*. 1988;39:135–144.
- Grant DG, Salassa JR, Hinni ML, Pearson BW, Perry WC. Carcinoma of the tongue Base treated by transoral laser microsurgery, part one: untreated tumors, a prospective analysis of oncologic and functional outcomes. *Laryngoscope*. 2006;116:2150–2155.
- Grant DG, Salassa JR, Hinni ML, Pearson BW, Hayden RE, Perry WC. Transoral laser microsurgery for carcinoma of the supraglottic larynx. *Otolaryngol-Head Neck Surg*. 2007;136:900–906.
- Steiner W, Ambrosch P, Hess CF, Kron M. Organ preservation by transoral laser microsurgery in piriform sinus carcinoma. *Otolaryngol-Head Neck Surg*. 2001;124:58–67.
- Steiner W, Fierek O, Ambrosch P, Hommerich CP, Kron M. Transoral laser microsurgery for squamous cell carcinoma of the base of the tongue. *Arch Otolaryngol Head Neck Surg*. 2003;129:36–43.
- Grant DG, Salassa JR, Hinni ML, Pearson BW, Hayden RE, Perry WC. Transoral laser microsurgery for recurrent laryngeal and pharyngeal cancer. *Otolaryngol Head Neck Surg*. 2008;138:606–613.
- Davis RK, Kriskovich MD, Galloway EB III, Buntin CS, Jepsen MC. Endoscopic supraglottic laryngectomy with postoperative irradiation. *Ann Otol Rhinol Laryngol*. 2004;113:132–138.
- Motta G, Esposito E, Cassiano B, Motta S. T1-T2-T3 glottic tumors: fifteen years experience with CO₂ laser. *Acta Otolaryngol Suppl*. 1997;527:155–159.
- Peretti G, Nicolai P, Piazza C, Redaelli de Zinis LO, Valentini S, Antonelli AR. Oncological results of endoscopic resections of Tis and T1 glottic carcinomas by carbon dioxide laser. *Ann Otol Rhinol Laryngol*. 2001;110:820–826.
- Steiner W, Ambrosch P. Endoscopic Laser Surgery of the Upper Aerodigestive Tract. New York: Thieme; 2000.
- Cohen JL, Clayman GL. *Atlas of Head and Neck Surgery* (Chapter 46, Figure 1.1-a). Clayman and Cohen; In Press (2011).
- Holsinger FC, Prichard CN, Shapira G, et al. Use of the photonic band gap fiber assembly CO₂ laser system in head and neck surgical oncology. *Laryngoscope*. 2006;116:1288–1290.
- Jacobson AS, Woo P, Shapshay SM. Emerging technology: flexible CO₂ laser WaveGuide. *Otolaryngol Head Neck Surg*. 2006;135:469–470.
- Ayari-Khalfallah S, Fuchsmann C, Froehlich P. Thulium laser in airway diseases in children. *Curr Opin Otolaryngol Head Neck Surg*. 2008;16:55–59.
- Koufman JA, Rees CJ, Frazier WD, et al. Office-based laryngeal laser surgery: a review of 443 cases using three wavelengths. *Otolaryngol Head Neck Surg*. 2007;137:146–151.
- Teichmann HO, Herrmann TR, Bach T. Technical aspects of lasers in urology. *World J Urol*. 2007;25:221–225.
- Dey P, Arnold D, Wight R, MacKenzie K, Kelly C, Wilson J. Radiotherapy versus open surgery versus endolaryngeal surgery (with or without laser) for early laryngeal squamous cell cancer. *Cochrane Database Syst Rev*. 2002;CD002027.
- Ogoltsova ES, Paches AI, Matyakin EG. Comparative evaluation of the efficacy of radiotherapy, surgery and combined treatment of stage I-II laryngeal cancer (T1-2N0M0) on the basis of co-operative studies. *J Otorhinolaryngol (Moscow)* 1990;3:3–37.
- Coman WB, Hendrkz JK, Hickey B, et al. Laser surgery for early glottic cancer. *ANZ Journal of Surgery*. 2003;73 (suppl 1):A57.
- Birchall M. EaStER—Early stage glottic cancer: endoscopic excision or radiotherapy: a feasibility study. National Research Register 2007;N0212194189.
- Gallo A, de Vincentiis M, Manciocco V, Simonelli M, Fiorella ML, Shah JP. CO₂ laser cordectomy for early-stage glottic carcinoma: a long-term follow-up of 156 cases. *Laryngoscope*. 2002;112:370–374.
- Motta G, Motta S, Testa D, Esposito E, Tartaro G. CO₂ laser surgery in the treatment of glottic cancer. *Head Neck* 2005;27:566–573.
- Ledda GP, Puxeddu R. Carbon dioxide laser microsurgery for early glottic carcinoma. *Otolaryngol Head Neck Surg*. 2006;134:911–915.
- Peretti G, Piazza C, Bolzoni A, et al. Analysis of recurrences in 322 Tis, T1, or T2 glottic carcinomas treated by carbon dioxide laser. *Ann Otol Rhinol Laryngol*. 2004;113:853–858.
- Eckel HE, Thumfart W, Jungehulsing M, Sittel C, Stennert E. Transoral laser surgery for early glottic carcinoma. *Eur Arch Otorhinolaryngol* 2000;257:221–226.
- Pradhan SA, Pai PS, Neeli SI, D'Cruz AK. Transoral laser surgery for early glottic cancers. *Arch Otolaryngol Head Neck Surg*. 2003;129:623–625.
- Grant DG, Salassa JR, Hinni ML, Pearson BW, Hayden RE, Perry WC. Transoral laser microsurgery for untreated glottic carcinoma. *Otolaryngol Head Neck Surg*. 2007;137:482–486.

29. Wang L, Liu J, Du J, Lu H, Hu M. [Oncologic outcome of carbon dioxide laser microsurgery for early glottic carcinoma]. *Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi*. 2007;21:985–987.
30. Stoeckli SJ, Guidicelli M, Schneider A, Huber A, Schmid S. Quality of life after treatment for early laryngeal carcinoma. *Eur Arch Otorhinolaryngol*. 2001;258:96–99.
31. Smith JC, Johnson JT, Cognetti DM, et al. Quality of life, functional outcome, and costs of early glottic cancer. *Laryngoscope*. 2003;113:68–76.
32. Loughran S, Calder N, MacGregor FB, Carding P, MacKenzie K. Quality of life and voice following endoscopic resection or radiotherapy for early glottic cancer. *Clin Otolaryngol*. 2005;30:42–47.
33. Cohen SM, Garrett CG, Dupont WD, Ossoff RH, Courey MS. Voice-related quality of life in T1 glottic cancer: irradiation versus endoscopic excision. *Ann Otol Rhinol Laryngol*. 2006;115:581–586.
34. Hinni ML, Salassa JR, Grant DG, et al. Transoral laser microsurgery for advanced laryngeal cancer. *Arch Otolaryngol Head Neck Surg*. 2007;133:1198–1204.
35. Mendenhall WM, Logan HL. Human papillomavirus and head and neck Cancer. *Am J Clin Oncol*. 2009;32(5):535–539.
36. Parsons JT, Mendenhall WM, Stringer SP, et al. Squamous cell carcinoma of the oropharynx: surgery, radiation therapy, or both. *Cancer*. 2002;94:2967–2980.
37. Grant DG, Hinni ML, Salassa JR, Perry WC, Hayden RE, Casler JD. Oropharyngeal cancer: a case for single modality treatment with transoral laser microsurgery. *Arch Otolaryngol Head Neck Surg*. 2009; Accepted for publication Sep 8, 2009.
38. Thomas L, Jones TM, Tandon S, Carding P, Lowe D, Rogers S. Speech and voice outcomes in oropharyngeal cancer and evaluation of the University of Washington Quality of Life speech domain. *Clin Otolaryngol*. 2009;34:34–42.
39. Gillison ML, D'Souza G, Westra W, et al. Distinct risk factor profiles for human papillomavirus type 16-positive and human papillomavirus type 16-negative head and neck cancers. *J Natl Cancer Inst*. 2008;100:407–420.
40. Chaturvedi AK, Engels EA, Anderson WF, Gillison ML. Incidence trends for human papillomavirus-related and -unrelated oral squamous cell carcinomas in the United States. *J Clin Oncol*. 2008;26:612–619.
41. Ryerson AB, Peters ES, Coughlin SS, et al. Burden of potentially human papillomavirus-associated cancers of the oropharynx and oral cavity in the US, 1998–2003. *Cancer*. 2008;113:2901–2909.
42. Machtay M, Moughan J, Trotti A, et al. Factors associated with severe late toxicity after concurrent chemoradiation for locally advanced head and neck cancer: an RTOG analysis. *J Clin Oncol*. 2008;26:3582–3589.
43. Larson DL, Kroll S, Jaffe N, Serure A, Goepfert H. Long-term effects of radiotherapy in childhood and adolescence. *Am J Surg*. 1990;160:348–351.
44. Herron DM, Marohn M. A consensus document on robotic surgery. *Surg Endosc*. 2008;22:313–325; discussion 311–312.
45. McLeod IK, Melder PC. Da Vinci robot-assisted excision of a vallecular cyst: a case report. *Ear Nose Throat J*. 2005;84:170–172.
46. Desai SC, Sung CK, Jang DW, Genden EM. Transoral robotic surgery using a carbon dioxide flexible laser for tumors of the upper aerodigestive tract. *Laryngoscope*. 2008;118:2187–2189.
47. Solares CA, Strome M. Transoral robot-assisted CO₂ laser supraglottic laryngectomy: experimental and clinical data. *Laryngoscope*. 2007;117:817–820.
48. Parmar A, Grant DG, Loizou P. Robotic surgery in ear nose and throat. *Eur Arch Otorhinolaryngol*. 2010;267(4):625–633.
49. Hockstein NG, Nolan JP, O'Malley BW Jr, Woo YJ. Robotic microlaryngeal surgery: a technical feasibility study using the daVinci surgical robot and an airway mannequin. *Laryngoscope*. 2005;115:780–785.
50. Hockstein NG, Nolan JP, O'Malley BW Jr, Woo YJ. Robot-assisted pharyngeal and laryngeal microsurgery: results of robotic cadaver dissections. *Laryngoscope*. 2005;115:1003–1008.
51. Haus BM, Kambham N, Le D, Moll FM, Gourin C, Terris DJ. Surgical robotic applications in otolaryngology. *Laryngoscope*. 2003;113:1139–1144.
52. Weinstein GS, O'Malley BW Jr, Hockstein NG. Transoral robotic surgery: supraglottic laryngectomy in a canine model. *Laryngoscope*. 2005;115:1315–1319.
53. McLeod IK, Mair EA, Melder PC. Potential applications of the da Vinci minimally invasive surgical robotic system in otolaryngology. *Ear Nose Throat J*. 2005;84:483–487.
54. Terris DJ, Haus BM, Gourin CG, Lilagan PE. Endorobotic resection of the submandibular gland in a cadaver model. *Head Neck*. 2005;27:946–951.
55. O'Malley BW Jr, Weinstein GS, Hockstein NG. Transoral robotic surgery (TORS): glottic microsurgery in a canine model. *J Voice*. 2006;20:263–268.
56. Weinstein GS, O'Malley BW Jr, Snyder W, Hockstein NG. Transoral robotic surgery: supraglottic partial laryngectomy. *Ann Otol Rhinol Laryngol*. 2007;116:19–23.

57. O'Malley BW Jr, Weinstein GS, Snyder W, Hockstein NG. Transoral robotic surgery (TORS) for base of tongue neoplasms. *Laryngoscope*. 2006;116:1465–1472.
58. Weinstein GS, O'Malley BW Jr, Snyder W, Sherman E, Quon H. Transoral robotic surgery: radical tonsillectomy. *Arch Otolaryngol Head Neck Surg*. 2007;133:1220–1226.
59. Faust RA, Rahbar R. Robotic surgical technique for pediatric laryngotracheal reconstruction. *Otolaryngol Clin North Am*. 2008;41:1045–1051, xi.
60. Ozer E, Waltonen J. Transoral robotic nasopharyngectomy: a novel approach for nasopharyngeal lesions. *Laryngoscope*. 2008;118:1613–1616.
61. Hanna EY, Holsinger C, DeMonte F, Kupferman M. Robotic endoscopic surgery of the skull base: a novel surgical approach. *Arch Otolaryngol Head Neck Surg*. 2007;133:1209–1214.
62. Hockstein NG, O'Malley BW Jr, Weinstein GS. Assessment of intraoperative safety in transoral robotic surgery. *Laryngoscope*. 2006;116:165–168.
63. Gagner M. Endoscopic subtotal parathyroidectomy in patients with primary hyperparathyroidism. *Br J Surg*. 1996;83(6):875.
64. Huscher CS, Chiodini S, Napolitano C, Recher A. Endoscopic right thyroid lobectomy. *Surg Endosc*. 1997;11:877.
65. Yoon JH, Park CH, Chung WY. Gasless endoscopic thyroidectomy via an axillary approach: experience of 30 cases. *Surg Laparosc Endosc Percutan Tech*. 2006;16:226–231.
66. Ikeda Y, Takami H, Sasaki Y, Kan S, Niimi M. Endoscopic resection of thyroid tumors by the axillary approach. *J Cardiovasc Surg (Torino)*. 2000;41:791–792.
67. Sasaki A, Nakajima J, Ikeda K, Otsuka K, Koeda K, Wakabayashi G. Endoscopic thyroidectomy by the breast approach: a single institution's 9-year experience. *World J Surg*. 2008;32:381–385.
68. Ohgami M, Ishii S, Arisawa Y, et al. Scarless endoscopic thyroidectomy: breast approach for better cosmesis. *Surg Laparosc Endosc Percutan Tech*. 2000;10:1–4.
69. Cho YU, Park IJ, Choi KH, et al. Gasless endoscopic thyroidectomy via an anterior chest wall approach using a flap-lifting system. *Yonsei Med J* 2007;48:480–487.
70. Inabnet WB III, Jacob BP, Gagner M. Minimally invasive endoscopic thyroidectomy by a cervical approach. *Surg Endosc*. 2003;17:1808–1811.
71. Miccoli P, Pinchera A, Cecchini G, et al. Minimally invasive, video-assisted parathyroid surgery for primary hyperparathyroidism. *J Endocrinol Invest*. 1997;20:429–430.
72. Ikeda Y, Takami H, Niimi M, Kan S, Sasaki Y, Takayama J. Endoscopic thyroidectomy by the axillary approach. *Surg Endosc*. 2001;15:1362–1364.
73. Strik MW, Anders S, Barth M, Barlehner E, Benecke C, Benhidjeb T. [Total videoendoscopic thyroid resection by the axillobilateral breast approach. Operative method and first results]. *Der Chirurg: Zeitschrift für alle Gebiete der operativen Medizin*. 2007;78:1139–1144.
74. Koh YW, Kim JW, Lee SW, Choi EC. Endoscopic thyroidectomy via a unilateral axillo-breast approach without gas insufflation for unilateral benign thyroid lesions. *Surg Endosc*. 2009;23:2053–2060.
75. Shimazu K, Shiba E, Tamaki Y, et al. Endoscopic thyroid surgery through the axillo-bilateral-breast approach. *Surg Laparosc Endosc Percutan Tech*. 2003;13:196–201.
76. Kim JS, Kim KH, Ahn CH, Jeon HM, Kim EG, Jeon CS. A clinical analysis of gasless endoscopic thyroidectomy. *Surg Laparosc Endosc Percutan Tech*. 2001;11:268–272.
77. Ikeda Y, Takami H, Niimi M, Kan S, Sasaki Y, Takayama J. Endoscopic thyroidectomy and parathyroidectomy by the axillary approach. A preliminary report. *Surg Endosc*. 2002;16:92–95.
78. Shimizu K, Tanaka S. Asian perspective on endoscopic thyroidectomy—a review of 193 cases. *Asian J Surg*. 2003;26:92–100.
79. Kang SW, Jeong JJ, Nam KH, Chang HS, Chung WY, Park CS. Robot-assisted endoscopic thyroidectomy for thyroid malignancies using a gasless transaxillary approach. *J Am Coll Surg*. 2009;209:e1–e7.
80. Lewis CM, Chung WY, Holsinger FC. Feasibility and surgical approach of transaxillary robotic thyroidectomy without CO(2) insufflation. *Head Neck*. 2010;32:121–126.
81. Bellantone R, Lombardi CP, Bossola M, et al. Video-assisted vs conventional thyroid lobectomy: a randomized trial. *Arch Surg*. 2002;137:301–304; discussion 305.
82. Lombardi CP, Raffaelli M, D'alatri L, et al. Video-assisted thyroidectomy significantly reduces the risk of early postthyroidectomy voice and swallowing symptoms. *World J Surg*. 2008;32:693–700.
83. Lombardi CP, Raffaelli M, Princi P, et al. Safety of video-assisted thyroidectomy versus conventional surgery. *Head Neck*. 2005;27:58–64.
84. Lai SY, Walvekar RR, Ferris RL. Minimally invasive video-assisted thyroidectomy: expanded indications and oncologic completeness. *Head Neck*. 2008;30:1403–1407.
85. Kim JH, Choi YJ, Kim JA, et al. Thyroid cancer that developed around the operative bed and subcutaneous tunnel

- after endoscopic thyroidectomy via a breast approach. *Surg Laparosc Endosc Percutan Tech*. 2008;18:197–201.
86. Lee YS, Yun JS, Jeong JJ, Nam KH, Chung WY, Park CS. Soft tissue implantation of thyroid adenomatous hyperplasia after endoscopic thyroid surgery. *Thyroid*. 2008;18:483–484.
 87. Wille G, Miccoli P. Re: soft tissue implantation of thyroid adenomatous hyperplasia after endoscopic thyroid surgery. *Thyroid*. 2009;19:313.
 88. Carreno OJ, Wilson WR, Nootheti PK. Exploring endoscopic neck surgery in a porcine model. *Laryngoscope*. 1999;109:236–240.
 89. Dulguerov P, Vaezi AE, Belenger J, et al. Endoscopic neck dissection in an animal model: comparison of nodal yield with open-neck dissection. *Arch Otolaryngol Head Neck Surg*. 2000;126:417–420.
 90. Dulguerov P, Leuchter I, Szalay-Quinodoz I, et al. Endoscopic neck dissection in human cadavers. *Laryngoscope*. 2001;111:2135–2139.
 91. Terris DJ, Monfared A, Thomas A, Kambham N, Saenz Y. Endoscopic selective neck dissection in a porcine model. *Arch Otolaryngol Head Neck Surg*. 2003;129:613–617.
 92. Holsinger FC, Sweeney AD, Jantharapattana K, et al. The emergence of endoscopic head and neck surgery. *Curr Oncol Rep* 2010;12:216–222.

CHAPTER 6

Incorporating Novel Agents With Chemotherapy and Radiotherapy for the Treatment of Locally Advanced Squamous Cell Carcinoma of the Head and Neck

Athanasios Kotsakis, Michael K. Gibson, and Athanassios Argiris

■ INTRODUCTION

Head and neck cancer represents the sixth most common cancer worldwide (1). Approximately 47 000 individuals are diagnosed with head and neck cancer in the United States and 76 000 in Europe on an annual basis (2,3). The majority of the patients present with locoregionally advanced disease (American Joint Committee on Cancer, 6th edition, stages III and IVA-B). About 90% to 95% of head and neck cancer cases are of squamous cell carcinoma histology. Currently, patients with early-stage squamous cell carcinoma of the head and neck (SCCHN) are treated with single-modality treatment, either radiotherapy (RT) or surgery, with 5-year survival rates that exceed 80%. For locoregionally advanced SCCHN, combined modality therapy, with combinations of surgery, RT, and chemotherapy is standard, with a 5-year survival rate of approximately 50% (2,4).

Risk factors for SCCHN include tobacco and alcohol consumption (5–7). Recently, human papillomavirus (HPV), mainly HPV type 16 and to a lesser extent type 18 and other types, has been identified as a causative factor for SCCHN (8). Up to 60% of oropharyngeal SCCHN are HPV positive, which is a favorable prognostic factor (9,10).

HPV-positive tumors have better responsiveness to RT, chemotherapy, or both, and might be more susceptible to immune surveillance of tumor-specific antigens than HPV-negative tumors (4).

■ STANDARD TREATMENT OF LOCALLY ADVANCED SCCHN

The management of locally advanced SCCHN represents a complex and challenging task. Traditionally, surgery, RT, and chemotherapy are the main treatment modalities. Locoregional recurrence is the most common type of treatment failure and death in patients with locally advanced SCCHN; however, distant metastases are also emerging as frequent sites of failure (11).

Several phase III clinical trials have shown that concomitant chemoradiotherapy (CRT) improves treatment efficacy results than RT alone or the sequential administration of chemotherapy and RT (4). The survival advantage seen with concomitant CRT in these trials has been predominantly attributed to improved locoregional control (LRC). In a meta-analysis of 63 trials with nearly 11 000 patients with SCCHN, the addition of

chemotherapy to RT resulted in an absolute survival improvement of 8% at 5 years (12). The results of this meta-analysis were confirmed in subsequent updated meta-analyses (13), the most recent of which analyzed 93 randomized trials and 17 346 patients (14). There has been great variability in the choice of chemotherapeutic regimen in CRT trials. However, RT with concurrent high-dose bolus cisplatin (100 mg/m² on days 1, 22, and 43 of RT) is a widely used regimen that has been proven in many multicenter phase III randomized trials. Although this regimen is efficacious, it is also associated with significant toxicities and is suitable for patients with good performance status and without severe comorbidities (15,16). In addition to the 3-weekly schedule, a variety of other cisplatin schedules of administration have been used (e.g., weekly) (17). Another widely used regimen is the combination of cisplatin and 5-fluorouracil (5-FU) (PF) concurrently with RT (18–20). Alternatively, carboplatin alone (21–23), carboplatin and 5-FU (24), hydroxyurea and 5-FU with or without paclitaxel (25), and cisplatin and paclitaxel (26) have been used concurrently with RT.

In case CRT is the primary treatment for SCCHN, salvage surgery is indicated for selected patients with residual or recurrent disease (27,28). In patients with SCCHN treated initially with surgery, postoperative CRT is employed for selected patients on the basis of high-risk pathologic features. Phase III clinical trials in this setting have revealed superiority of postoperative CRT over RT alone in terms of LRC, disease-free survival (DFS), and/or OS (29–31).

A major goal in the management of patients with SCCHN is to achieve organ preservation, when it is possible and desirable. Patients with resectable cancers of the hypopharynx and larynx are potential candidates for laryngeal preserving treatment. Two pivotal randomized trials compared surgery followed by adjuvant RT with induction chemotherapy (IC) with PF followed by RT, respectively, in patients with locally advanced but resectable laryngeal and hypopharyngeal SCCHN. These studies demonstrated that survival was similar among the 2 groups of patients, although

laryngeal preservation was feasible in the majority of patients treated with a nonsurgical approach (32,33). A subsequent phase III randomized trial (Radiation Therapy Oncology Group [RTOG] 91–11 trial) evaluated 3 nonsurgical treatment options for locally advanced laryngeal SCCHN: IC with cisplatin and 5-FU followed by definitive RT, CRT with concurrent cisplatin, and definitive RT alone. This study showed that laryngeal preservation was significantly higher with concurrent CRT; however, there was no difference in OS between the treatment arms (16,34).

More recently, the combination of RT plus cetuximab, a monoclonal antibody against the epidermal growth factor receptor (EGFR), was proved superior to RT alone in patients with oropharyngeal, laryngeal, and hypopharyngeal SCCHN (35). The results of this study are discussed in detail here.

■ INDUCTION CHEMOTHERAPY

There is a strong rationale for the use of chemotherapy in the neoadjuvant (or induction) setting prior to definitive locoregional treatment. Distant as well as LRC can be potentially improved with this approach. The combination of cisplatin and 5-FU has been a commonly used and active induction regimen with overall response rates (RRs) of about 80% and complete response (CR) rates of about 30% (36). Meta-analyses have reported a marginal survival benefit from IC with PF, which was smaller than the effect on survival observed with concomitant CRT (14). However, many of these studies showed that induction therapy contributed to the reduction of distant metastases (32,37–41). In recent years, more potent induction regimens have been developed with the incorporation of a taxane (paclitaxel or docetaxel) to the PF regimen. Randomized trials have shown superiority in terms of survival or laryngeal preservation with PF plus a taxane versus PF alone (42–45). As a result, IC prior to CRT is being evaluated as an attractive approach for the treatment of locally advanced SCCHN in randomized clinical trials (46).

Incorporation of Novel Agents into Combined Modality Regimens

Although concomitant CRT has become standard for the treatment of locally advanced SCCHN, it is associated with increased toxicities compared with RT alone. Moreover, efficacy results remain suboptimal. The incorporation of novel agents offers the potential of enhancing efficacy without increasing toxicity. Several completed, ongoing, and planned clinical trials have investigated the incorporation of novel agents into combined modality regimens. In most of these studies, the novel agent is added onto a platform of standard RT plus platinum-based chemotherapy, whereas in some studies, a novel agent has been added to induction regimens. There are several challenges in the evaluation of new agents in combination with RT or CRT. Safety data with novel combinations are usually required before launching large phase II or phase III trials in patients with potentially curable SCCHN. Moreover, the determination of biomarkers that can predict the outcome of such therapies is essential but often elusive. Herein, we review each class of targeted agents separately with a focus on the integration of novel agents into the CRT regimens. Many of the studies reviewed have only been presented in abstract form, and in some cases, results should be interpreted with caution. However, it also suggests that this is a rapidly evolving field that has become the subject of intense clinical investigation in recent years.

Novel Antifolates: Pemetrexed

Pemetrexed, a novel multitargeted antifolate, inhibits several key enzymes involved in nucleotide synthesis, such as thymidylate synthetase, dihydrofolate reductase, and glycinamide ribonucleotide formyl transferase (47). Pemetrexed, is approved by the U.S. Food and Drug Administration (FDA) for the treatment of non-small cell lung cancer as well as mesothelioma (48–50). In preclinical models, pemetrexed has shown synergistic activity

with radiation (51–53). In a clinical study, the combination of pemetrexed with carboplatin and radiation was well tolerated and active in patients with advanced non-small cell lung and esophageal cancers (54). Pemetrexed has been used in patients with recurrent or metastatic SCCHN with encouraging results. A phase II clinical trial of pemetrexed in 35 patients with recurrent or metastatic SCCHN reported an RR of 26.5% and median time to progression of 3.9 months (55). Our group at the University of Pittsburgh has conducted a phase I study with pemetrexed added to standard RT and cetuximab in patients with head and neck cancers, the majority of whom had SCCHN (56). Pemetrexed was escalated on 3 dose levels (200, 300, and 500 mg/m²) in 2 parallel cohorts of patients, not previously irradiated (group A, *n* = 23) and previously irradiated (group B, *n* = 9). Neutropenic fever was dose limiting and necessitated the addition of prophylactic antibiotics. Grade 3 mucositis was common. The maximum tolerated dose (MTD) of pemetrexed was 500 mg/m² in group A and 350 mg/m² in group B. Among 13 patients with locally advanced, stage IV SCCHN who completed RT, 6 (46%) remained progression free after a median follow-up of 3 years; only 2 of them recurred locoregionally. In another phase II trial in recurrent or metastatic SCCHN, we reported promising efficacy results with the combination of pemetrexed and bevacizumab (57). These encouraging results led us to further investigate pemetrexed-containing regimens. We are currently conducting a phase II randomized study with RT/pemetrexed/cetuximab with or without bevacizumab in patients with locally advanced SCCHN (NCT00703976).

Agents Targeting Hypoxic Cells: Tirapazamine

Tirapazamine (TPZ) (SR-4233) is a novel anticancer drug that is activated to a toxic radical under hypoxic conditions. Tumor hypoxia, which is common in solid tumors, leads to resistance to radiation

and chemotherapy. Thus, the combination of conventional treatment with TPZ can potentially overcome treatment resistance. The combination of TPZ with cisplatin and concurrent RT was tested in phase I and II trials with promising results (58–60). In a phase II randomized trial, 122 patients were randomized to receive either 5-FU/cisplatin/RT or TPZ/cisplatin/RT. The 3-year failure-free survival rates were 55% for the TPZ/CRT arm and 44% for the CRT alone arm. Grade 3 or 4 mucositis and febrile neutropenia were more common in the TPZ group (60). Based on these results, the Trans-Tasman Radiation Oncology Group (TROG) conducted a phase III trial that compared concomitant cisplatin and RT with or without TPZ. A total of 861 patients from 89 sites in 16 countries were recruited in that study (TROG 02.02 or HeadSTART). However, the addition of TPZ to standard CRT did not improve any efficacy outcomes. The 2-year survival was approximately 66% in either arm; locoregional failure and failure-free survival were also similar between the 2 arms (61). Study results may have been affected by deviations in scheduled RT treatment plan that occurred in approximately 20% of patients and had an adverse impact on treatment outcomes. The results of another phase III randomized trial of TPZ in patients with SCCHN (TRACE) are still pending and are required to draw final conclusions about the role of TPZ in this disease (NCT00174837).

Epidermal Growth Factor Receptor Inhibitors

EGFR is the first member of the human epidermal growth factor receptor (HER)/Erb-B family of receptor tyrosine kinases that transduces extracellular signals to intracellular signaling pathways. It plays a key role in major cellular functions such as survival, apoptosis, and proliferation. EGFR signaling activation begins with the binding of its natural ligands (e.g., EGF and transforming growth factor α) to the membrane receptor that results in its homo- and heterodimerization with other receptors of the HER family (e.g., HER-2), which triggers a cascade of downstream effects (62) (Figure 6.1). Four primary signaling pathways have been implicated

in downstream EGFR signaling: a) Ras-mitogen-activated protein kinase, b) phosphatidylinositol-3-kinase Akt, c) phospholipase-C gamma (PLC- γ), and d) signal transducers and activators of transcription pathways (63). EGFR is upregulated in more than 90% of SCCHN. Increased levels of EGFR and/or its ligands have been correlated with worse patient outcome (64,65). The central role of EGFR in the biology of SCCHN suggests that blockade of EGFR is an attractive strategy for the treatment of SCCHN (66). Biological consequences of EGFR targeting include inhibition of cellular proliferation and proapoptotic and antiangiogenic effects (67–70).

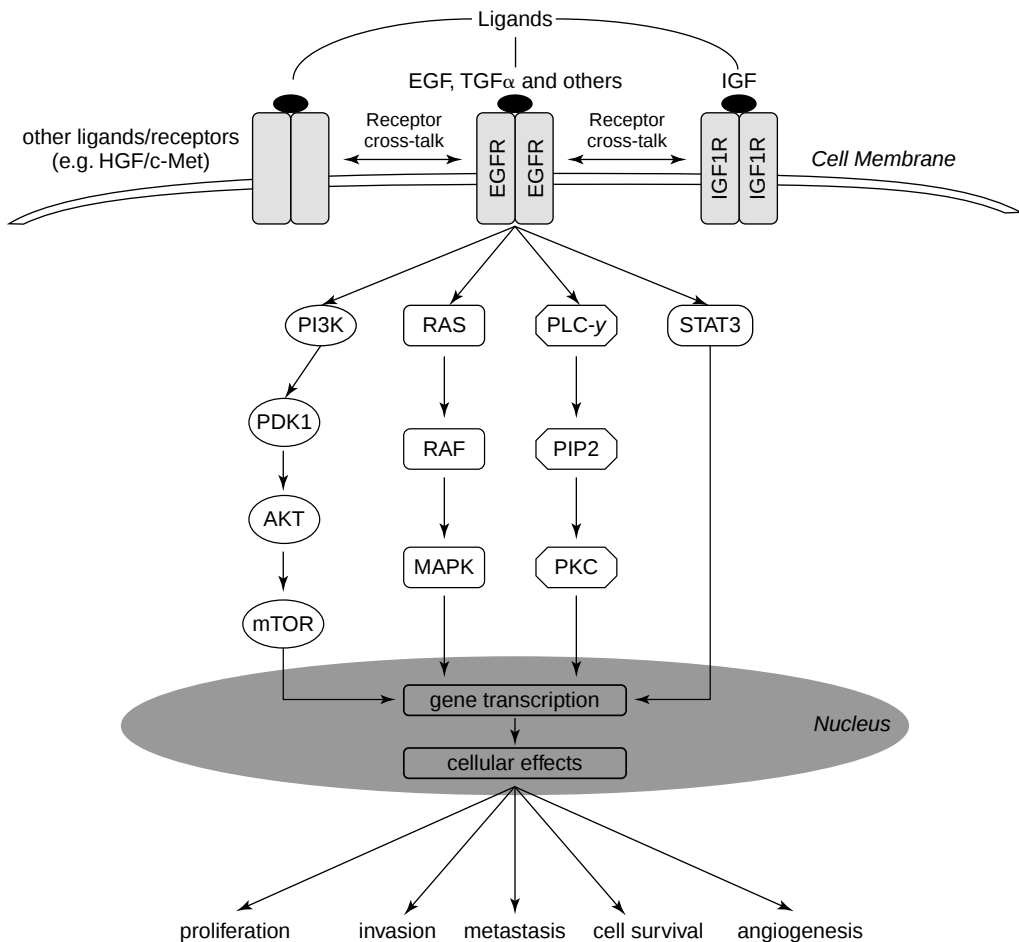
Anti-EGFR agents that have been extensively studied in the clinic can be divided into 2 major categories: a) monoclonal antibodies (moAbs), such as cetuximab, panitumumab, zalutunumab, pertuzumab, and h-R3/nimotuzumab, which act at the extracellular domain of the receptor (71), and b) tyrosine kinase inhibitors (TKIs), such as erlotinib, gefitinib, and lapatinib, which act on the cytosolic ATP-binding domain of EGFR to inhibit EGFR autophosphorylation (71).

Monoclonal Antibodies Against EGFR

Monoclonal antibodies against EGFR inhibit activation of distinct EGFR signaling pathways and inhibit SCCHN growth through cell cycle arrest, pro-apoptotic effect, and inhibition of angiogenesis, invasion and metastasis, and possibly immune mechanisms (72,73). Moreover, anti-EGFR antibodies can augment the antitumor activity of RT and chemotherapy (74–77).

Cetuximab

Cetuximab is a chimeric human-murine monoclonal antibody that binds competitively to the EGFR with a higher affinity than its endogenous ligands. It has been studied extensively in SCCHN in several phase II and III studies and was approved by the FDA, in combination with RT for the treatment of patients with locally advanced head and neck cancer. A pivotal multicenter phase III study compared RT alone (arm A, $n = 213$ patients) with RT in combination with weekly cetuximab

**FIGURE 6.1**

Epidermal growth factor receptor (EGFR) signaling pathway. EGFR is activated by the binding of natural ligands [e.g. epidermal growth factor (EGF) and transforming growth factor- α (TGF- α)] to the transmembrane receptor that results in its homo- and/or hetero-dimerization with other receptors of the HER family (e.g. HER-2). The signal is transduced to the nucleus via several intracellular pathways leading to various cellular and tissue effects, as shown in the figure. EGFR signaling may be modulated by cross-talk with other receptors, such as the insulin-like growth factor receptor 1 (IGF1R) and c-met.

250 mg/m² given during RT after an initial dose of 400 mg/m² the week prior to starting RT (arm B, $n = 211$ patients) (35). The majority of patients had oropharyngeal cancer, whereas the patients with oral cavity primaries were not included. Patients treated with cetuximab had significantly prolonged OS with a 26% reduction in the risk of death (hazard ratio [HR], 0.74; 95% confidence interval [CI], 0.57–0.97) and a 10% absolute benefit in OS rate

at 5 years (78). LRC was also superior with cetuximab (HR, 0.68; 95% CI, 0.52–0.89 [$P = 0.005$]), however, there was no significant difference in terms of distant control between the 2 arms. A common toxicity in patients who received cetuximab was acneiform rash. Infusion-related reactions were also seen. However, in-field toxicities, such as mucositis and dermatitis, did not increase with the addition of cetuximab to RT. Quality-of-life parameters were

not adversely affected by the addition of cetuximab (79). This study was initiated prior to the wide adoption of concomitant CRT as standard and used RT alone as control, whereas it allowed different RT fractionation regimens. Currently, the combination of cetuximab with RT is considered an alternative to platinum-based CRT or RT alone for the treatment of locally advanced SCCHN, particularly for the elderly or for patients with severe comorbidities or poor performance status.

Multiple phase II studies have investigated the integration of cetuximab to standard platinum-based CRT (80,81). An initial concern about increased toxicities with accelerated fractionation by concomitant boost RT and cisplatin plus cetuximab (80) was not replicated in subsequent studies. The combination of cisplatin (75 mg/m^2 every 3 weeks $\times$ 3) and cetuximab concurrently with standard RT was evaluated in a phase II cooperative group trial in patients with unresectable locally advanced SCCHN (E3303; NCT 00096174). One death attributed to the treatment was reported. Grade 3 or 4 toxicities included neutropenia (26%), rash (28%), dermatitis (15%), and mucositis (54%). Forty-eight percent of the patients had an objective response after treatment completion. The 1-year OS was 76% and the median OS was 33 months (82) (see Table 6.1), which appear superior to survival outcomes reported by the previous intergroup phase III study with RT and cisplatin in the same patient population (15). Cetuximab has also been combined with weekly cisplatin 30 mg/m^2 and concurrent RT in a study by the RTOG in the postoperative setting (RTOG 0234) (83), a phase II trial in nasopharyngeal carcinoma (84), as well as a study from the University of Pittsburgh after induction therapy (85) (included in Table 6.1).

The RTOG 0234 study enrolled patients with high-risk resected SCCHN (83). Patients were randomized to receive RT (60 Gy) and weekly cetuximab over 6 weeks in combination with either weekly cisplatin 30 mg/m^2 or weekly docetaxel 15 mg/m^2 . Two-hundred thirty-eight patients were enrolled. Ninety-four percent of patients had pathologic stage IV disease and 47% had an oral cavity

primary. Toxicities were predictable and comparable between the 2 arms; grade 3 or 4 myelosuppression was seen in 28% versus 14% of patients and grade 3 or 4 mucositis in 37% and 33% of patients in the cisplatin and docetaxel groups, respectively, and dermatitis in 39% of patients in each group. There was 1 treatment-related death in each arm. With a median follow-up of 30 months, the 2-year survival rates in the cisplatin and docetaxel arms were 69% and 79%, respectively. The 2-year DFS also favored numerically the docetaxel arm (66% for docetaxel and 57% for cisplatin), apparently due to better distant control with docetaxel; at 2 years the distant metastasis rate was 26% for the cisplatin arm versus 13% for the docetaxel arm. DFS from this trial was compared to a historical control of RT plus cisplatin from a previous RTOG trial (RTOG 9501); the HR for DFS was 0.85 and 0.72 with a corresponding absolute improvement at 2-year DFS of 2% and 11% in the cisplatin and docetaxel arms, respectively. DFS results in the docetaxel arm but not in the cisplatin arm were statistically better than the historical control ($P = 0.03$) (83). Therefore, additional studies of chemotherapy plus cetuximab are warranted in the postoperative CRT setting.

RTOG has recently completed accrual to a phase III study that compared accelerated fractionation by concomitant boost RT and cisplatin with or without cetuximab in patients with previously untreated, locally advanced SCCHN (RTOG 0522; NCT00265941). Results of this study are eagerly awaited and may define a new treatment standard.

Preliminary results from a European phase II study (TREMPIN) that compared RT plus high-dose cisplatin with RT plus cetuximab after IC with cisplatin, docetaxel, and 5-FU (TPF) were recently reported (86). One-hundred fifty-three patients with stage III/IV laryngeal or hypopharyngeal cancer were enrolled in the study. The primary end point was laryngeal preservation. Treatment consisted of 3 cycles of IC with TPF followed by cisplatin/RT (arm A) or cetuximab/RT (arm B). Patients who did not respond to TPF (less than 50% response) were to undergo salvage surgery. The overall response rate (ORR) to TPF

TABLE 6.1

Selected phase II trials of cetuximab in previously untreated locally advanced SCCHN

Treatment Regimen	Patient Population	Primary End Point/Sample Size	Main Findings/Comments	Author/Reference
CETUXIMAB AS PART OF IC AND SUBSEQUENT CRT				
IC: docetaxel, cisplatin, and cetuximab (TPE) for 3 cycles CRT: RT plus cisplatin and cetuximab Maintenance: cetuximab for 6 months	92% stage IVA-B 59% oropharynx	RR after IC ($n = 39$)	- RR: 86% after IC and 100% after CRT - CR: 5% after IC and 24% after CRT 2-year PFS and OS: 80% and 88% - Grade 3/4 neutropenia 77% and febrile neutropenia 10% during IC; grade 3/4 mucositis 51% and grade 3/4 dermatitis 27% during CRT	Argiris et al (85)
IC: docetaxel, cisplatin, and 5-FU (TPF) plus cetuximab $\times$ 4 cycles CRT: RT plus cetuximab	Unresectable 100% stage IVA-B 48 % oropharynx	RR after 2 vs. 4 cycles of IC ($n = 50$)	- RR: 76% after 2 cycles and 78% after 4 cycles of IC - CR 14% after 2 cycles IC and 24% after 4 cycles IC - Febrile neutropenia (26%) during IC	Mesia et al (92)
IC: weekly paclitaxel, carboplatin plus cetuximab (6 weeks) CRT: RT plus weekly paclitaxel, carboplatin, and cetuximab Maintenance: cetuximab for 6 months (E2303)	Stage III-IV, resectable SCCHN >50% oropharynx	1-year EFS ($n = 74$)	66 evaluable pts (completed IC) 55 pts completed CRT - Pathologic CR: 62.5% after induction and 97% after CRT - Grade 3/4: mucositis/stomatitis (32%) and neutropenia (31%), rash (9%), radiation dermatitis (13%)	Wanebo et al (90)
CETUXIMAB INTO IC ONLY				
IC: weekly paclitaxel, carboplatin plus cetuximab (6 weeks) CRT: variable	100% stage IV 89% oropharynx	CR rate after IC ($n = 47$)	- RR: 98%, CR: 26% after IC - Grade 3/4 rash (47%) and neutropenia (34%) during induction	Kies et al (89)

(continued)

TABLE 6.1 Continued

Treatment Regimen	Patient Population	Primary End Point/Sample Size	Main Findings/Comments	Author/Reference
CETUXIMAB INTO CRT WITHOUT IC				
RT plus cisplatin and cetuximab (E3303)	Unresectable 98% stage IV 68% oropharynx	2-year PFS (<i>n</i> = 69)	- Grade 3/4 toxicities: dysphagia (45%), mucositis (55%), anemia (8%), neutropenia (26%), anorexia (37%), rash (28%) - Grade 5 toxicity: 2 pts (1 pt with neutropenic fever) - RR: 48% 1-year OS: 76%; median OS: 33 months	Langer et al (82)
RT plus 5-FU, hydroxyurea (FHx), and cetuximab every other week (IC allowed)	94% stage IVA-B 45% oropharynx 70% underwent IC	LRC, distant control, OS (<i>n</i> = 33)	- Common grade 3 or 4 toxicities: mucositis (33%), dermatitis (15%), neutropenia (9%) 1-year LRC: 91%	Kao et al (87)
RT plus cisplatin and cetuximab (arm A) versus RT plus docetaxel and cetuximab (arm B) (RTOG 0234) Phase II randomized study in the postoperative setting	High-risk resected 94% stage IV 47% oral cavity	DFS (<i>n</i> = 238; data presented in 203 pts, 97 in arm A and 106 in arm B)	2-year OS: arm A (69%), arm B (79%) 2-year DFS: arm A (57%), arm B (66%) 2-year distant metastasis: arm A (26%), arm B (13%) - Similar toxicities in the 2 arms	Kies et al (83)
CETUXIMAB VERSUS CISPLATIN AFTER IC				
IC: docetaxel, 5-FU, and cisplatin (TPF) CRT: RT plus cisplatin (arm A) versus RT plus cetuximab (arm B) Phase II randomized study (TREMPLIN)	Stage III/IV laryngeal or hypopharynx	LP at 3 months (<i>n</i> = 153)	74% received the planned IC 85% RR to IC 115 pts randomized to arm A (59 pts) or to arm B (56 pts) - Comparable LP (93% vs 96%) long-term efficacy results pending - More toxicities related to cisplatin	Lefebvre et al (86)

CR, complete response; LP, laryngeal preservation; PR, partial response; OS, overall survival; IC, induction chemotherapy; LRC, locoregional control; LRF, locoregional failure; DC, disease control; CRT, chemoradiotherapy; EFS, event-free survival; DFS, disease-free survival; PFS, progression-free survival; RR, response rate; RT, radiotherapy; SCCHN, squamous cell carcinoma of the head and neck; pts, patients; 5-FU, 5-fluorouracil.

induction was 85%. One-hundred sixteen patients were randomly assigned to 1 of the 2 treatment arms. There was no difference between RT/cisplatin and RT/cetuximab in terms of 3-month laryngeal preservation; however, RT/cetuximab was better tolerated, which improved treatment delivery: 71% of patients completed treatment per protocol in arm B versus 43% in arm A. Induction TPF affected the ability to safely deliver cisplatin during RT. Nine patients developed permanent renal failure with RT/cisplatin, which seems to be related to a cumulative effect of cisplatin (86).

Finally, cetuximab has been combined with nonplatinum CRT regimens, such as RT plus 5-FU and hydroxyurea, with promising preliminary results (NCT00462735) (87) (see Table 6.1).

Cetuximab as Part of Induction Regimens

Cetuximab can augment the efficacy of chemotherapy as shown in a phase III trial in recurrent or metastatic SCCHN ("EXTREME" study). In this study, 442 patients with previously untreated recurrent or metastatic SCCHN were randomly assigned to receive a platinum-based doublet (cisplatin or carboplatin plus 5-FU) with or without cetuximab (88). The addition of cetuximab to platinum and 5-FU significantly prolonged the median OS from 7.4 to 10.1 months, with a reduction in the risk of death of 20% (HR, 0.80; 95% CI, 0.64–0.99 [$P = 0.04$]). Also, the addition of cetuximab to platinum and 5-FU improved the median progression-free survival (PFS) from 3.3 to 5.6 months (HR for progression, 0.54; $P < 0.001$) and the objective RR from 20% to 36% ($P < 0.001$). Toxicities observed in cetuximab-treated patients were as expected: 9% had grade 3 skin reactions and 3% had grade 3 or 4 infusion-related reactions. Sepsis occurred in 9 patients in the cetuximab group and in 1 patient in the chemotherapy-alone group ($P = 0.02$), but there were no cetuximab-related deaths.

Cetuximab has been incorporated into induction therapy regimens for the treatment of locally advanced SCCHN. Five clinical trials of cetuximab plus platinum and taxane-containing platform

regimens, including a) carboplatin and paclitaxel, b) cisplatin and docetaxel, and c) TPF, have reported results (85,89–92).

In a phase II study conducted at the MD Anderson Cancer Center, 47 patients were treated with paclitaxel 135 mg/m², carboplatin area under the curve (AUC) 2, and cetuximab weekly for 6 weeks followed by locoregional therapy with surgery, RT, or CRT customized on presenting T stage and tumor site at presentation. Approximately 50% of patients developed severe rash and 34% grade 3 or 4 neutropenia (prophylactic granulocyte colony-stimulating factor [G-CSF] was used). The regimen was highly active with an overall RR of 98%, including 26% CRs. In all, 81% of patients achieved CR in the primary site and 28% in the neck nodes. At the time of the preliminary report, 4 patients had disease recurrence after a median follow-up of 10 months, including 3 with distant metastases (89).

The same induction regimen with weekly carboplatin, paclitaxel, and cetuximab was employed in a phase II study conducted by the Eastern Cooperative Oncology Group (ECOG) (E2303) (90). In this study, supportive G-CSF treatment was not allowed and the dose of paclitaxel had to be reduced from 135 to 90 mg/m² due to considerable hematologic toxicities with the higher dose. A biopsy of the primary site was done after completion of induction and prior to starting CRT at week 8, if there was a clinical response, and at week 14, that is, after the first 5 weeks of CRT. Biopsy-negative patients continued to receive CRT to a total dose of 68–72 Gy, whereas biopsy-positive patients underwent salvage surgery. Maintenance cetuximab was then administered to all patients for 6 months. The primary end point was 1-year event-free survival rate, with pathologic RR as a secondary end point. Seventy-four patients with locally advanced but resectable SCCHN were enrolled; 66 patients (89%) completed the induction regimen and 55 patients completed CRT to 68–72 Gy. Forty patients underwent biopsy after induction and 25 had negative biopsies, whereas 31 patients had a restaging at week 14 of whom only 1 had persistent

tumor (90). These findings indicate that induction with cetuximab plus paclitaxel/carboplatin followed by the same agents with concurrent RT produces a high rate of pathologic CR at the primary tumor site. The usefulness of a biopsy after induction or at 50 Gy of CRT in determining the need for salvage surgery requires validation in future studies.

Our group at the University of Pittsburgh has conducted a study of induction therapy with docetaxel, cisplatin, and cetuximab (TPE) followed by RT, cisplatin, and cetuximab (XPE) and followed by maintenance cetuximab for 6 months (85). Thirty-six patients received all 3 cycles of chemotherapy, and 33 completed XPE per protocol; 31 patients received maintenance cetuximab with a median duration of 5 months. In 37 evaluable patients, the overall objective response using Response Evaluation Criteria In Solid Tumors (RECIST) was 86% (with 5% CRs) and 100% (with 24% CR) after TPE and XPE, respectively. Using positron emission tomography scan, 59% of patients had a CR in the primary site after TPE and 77% after XPE. With a median follow-up of 16 months, the 2-year PFS was 80%; most relapses were in locoregional sites (5 locoregional versus 1 distant). Hematological toxicity was common during TPE, mainly neutropenia (10% incidence of neutropenic fever). Grade 3 or 4 hypomagnesemia was common during XPE (36%), whereas mucositis was seen in 51% and dermatitis in 27% of patients (85). This regimen resulted in expected toxicities and was highly efficacious and warrants testing in larger multicenter trials.

The combination of TPF with cetuximab in the induction therapy setting has been investigated in a phase I study conducted at the Dana Farber Cancer Institute. Twenty-eight evaluable patients with locally advanced SCCHN were enrolled; 71% of patients had oropharyngeal cancer of whom 65% had HPV-positive tumors; 92% of all patients had stage IV disease. Cisplatin and docetaxel were administered at fixed doses, 100 and 75 mg/m², respectively, whereas 5-FU was dose escalated from 700 to 1000 mg/m² as a continuous infusion over 4 days. This regimen was associated with

gastrointestinal toxicities, such as mucositis and diarrhea, and febrile neutropenia. A 5-FU dose of 850 mg/m² was considered as MTD. This regimen was very active. All 28 evaluable patients achieved a radiographic partial response (PR). Moreover, 20 patients underwent biopsy after induction therapy and 16 (80%) had a pathologic CR (91).

Results from a phase II study that evaluated the combination of cetuximab with TPF were recently reported as well (92). Fifty patients with previously untreated, unresectable SCCHN received weekly cetuximab, cisplatin 75 mg/m² on day 1, docetaxel 75 mg/m² on day 1, and 5-FU 750 mg/m² as a continuous infusion for 5 days, with G-CSF and antibiotic prophylaxis, followed by accelerated boost RT with concurrent cetuximab. The ORR was 76% and 78% after 2 and 4 cycles of induction therapy, respectively. Furthermore, the rate of CR was higher in patients who received more cycles of therapy (24% vs. 14%) (92).

Currently, a number of phase III studies of cetuximab in patients with locally advanced SCCHN are ongoing (see Table 6.2).

Panitumumab

Panitumumab (ABX-EGF) is a fully human IgG2 antibody that binds with high affinity to the EGFR, which may have a lower incidence of infusion reactions due to the lack of mouse protein. Panitumumab has been evaluated in preclinical studies for SCCHN (93,94). These studies showed a favorable interaction between panitumumab and RT in both in vitro and in vivo models. A phase I study of panitumumab in combination with CRT was presented (95). Nineteen patients with previously untreated stage III or IVA SCCHN (15 with oropharyngeal primaries, including 7 with documented HPV-positive tumors) received RT with concurrent weekly carboplatin AUC 1.5 plus panitumumab 2.5 mg/kg plus paclitaxel at 2 dose levels, 15 and 30 mg/m². Of 16 patients treated at the higher paclitaxel dose, 1 developed febrile neutropenia, which was considered dose limiting. Dysphagia grade 3 (95%), mucositis grade 3 or 4 (85%), and grade 3 dermatitis (42%) were

TABLE 6.2

Ongoing or recently completed phase III randomized trials of cetuximab in locally advanced SCCHN

Treatment Regimens	Location/Sponsor	Primary End Point	Sample Size	ClinicalTrials.gov Identifier
Accelerated concomitant boost RT/cisplatin versus accelerated concomitant boost RT/cisplatin/cetuximab (RTOG 0522)	United States; Radiation Therapy Oncology Group/ National Cancer Institute	PFS	945	NCT00265941
RT 70 Gy/carboplatin/5-FU/cetuximab versus RT 70 Gy/cetuximab (GORTEC2007-01)	France; Groupe Oncologie Radiotherapie Tete et Cou	PFS	406	NCT00609284
IC: cisplatin/docetaxel/5-FU (in both arms) CRT: RT 70 Gy/cisplatin versus RT 70 Gy/cetuximab	Spain; Grupo Español de Tratamiento de Tumores de Cabeza y Cuello	OS	458	NCT00716391

CRT, chemoradiotherapy; RT, radiotherapy; PFS, progression-free survival; OS, overall survival; DFS, disease-free survival; IC, induction chemotherapy; 5-FU, 5-fluorouracil.

common adverse events at both paclitaxel dose levels. However, gastrostomy tubes were eventually removed from all patients. All patients, many of whom had favorable prognosis disease, achieved a PR using RECIST, whereas 69% of 13 evaluable patients had a CR in the primary (95). Several other trials with panitumumab in combination with CRT are currently ongoing (see Table 6.3).

Zalutumumab

Zalutumumab (HuMax-EGFr) is a fully human, high-affinity IgG1 monoclonal antibody that targets EGFR (96). The results of a phase I/II study with zalutumumab monotherapy in patients with recurrent or metastatic SCCHN after failure of conventional treatment were reported (97). Twenty-seven patients received intravenous infusions of zalutumumab at 6 escalated dose levels, from 0.15 to 8 mg/kg. Twenty-eight days after the initial single dose of zalutumumab, patients received 4 weekly infusions at the same dose. Dose-dependent acneiform rash but no dose-limiting toxicity was observed. Only 1 patient developed

grade 3 rash. Other toxicities included rigors, fever, nausea, and flushing. A partial objective response was seen in 2 patients (at doses of 1 and 8 mg/kg) (97). Table 6.3 shows ongoing trials of zalutumumab in patients with locally advanced SCCHN.

Nimotuzumab

Nimotuzumab (h-R3) is a humanized IgG1 monoclonal antibody against EGFR with less affinity to EGFR than cetuximab. It is well tolerated as a single agent at weekly doses up to 400 mg and is associated with a very low incidence of rash (98). In a phase I/II trial that enrolled 24 patients with unresectable SCCHN, 6 weekly infusions of nimotuzumab were administered concurrently with standard fractionation RT to a total dose of 60 to 66 Gy (99). A second biopsy was obtained in a small number of patients ($n = 9$) on week 3 of treatment in order to evaluate the antiproliferative and antiangiogenic activity of the regimen on tumor tissue. The combination was well tolerated without the development of skin toxicities. The most common adverse events were tremors, fever,

TABLE 6.3

Selected ongoing trials of anti-EGFR antibodies other than cetuximab in locally advanced SCCHN

Regimen	Phase	Location/ Sponsor	Primary End Point	ClinicalTrials.gov Identifier
PANITUMUMAB				
Concurrent with RT: cisplatin versus panitumumab	III	National Cancer Institute of Canada	PFS	NCT00820248
Concurrent with RT: cisplatin versus cisplatin plus panitumumab	I/II	Multicenter (Amgen)	LRC	NCT00500760
Concurrent with RT: cisplatin versus panitumumab	I/II	Multicenter (Amgen)	LRC	NCT00547157
Concurrent with postoperative RT: cisplatin plus panitumumab	II	University of Pittsburgh	DFS	NCT00798655
ZALUTUMUMAB				
Concurrent with RT: zalutumumab/ cisplatin	I/II	Multicenter (Genmab)	Safety	NCT00401401
Concurrent with RT: Zalutumumab	I/II	Multicenter (Genmab)	Safety	NCT00707655
RT (plus weekly cisplatin for stage III/IV) versus RT (plus weekly cisplatin for stage III/IV) plus zalutumumab	III	Danish Head and Neck Cancer Group (DAHANCA 19)	LRC	NCT00496652
NIMOTUZUMAB				
IC: cisplatin/5-FU plus nimotuzumab	II	Fudan University, China	ORR	NCT00910117
Concurrent with RT: cisplatin plus nimotuzumab	II	National Cancer Center, Singapore	ORR	NCT00702481
Concurrent with postoperative RT: cisplatin plus placebo versus cisplatin plus nimotuzumab	III	National Cancer Centre, Singapore	DFS	NCT00957086

CRT, chemoradiotherapy; RT, radiotherapy; PFS, progression-free survival; OS, overall survival; ORR, overall response rate; DFS, disease-free survival; LRC, locoregional control; IC, induction chemotherapy; 5-FU, 5-fluorouracil.

hypotension, dermatitis, mucositis, and dysphagia. On repeat tumor biopsies, there was evidence of decreased proliferative activity, as evaluated by Ki67 staining, and reduced vascularity. Fourteen (87.5%) of 16 evaluable patients responded, and 9 of them completely (CR), at the 2 higher dose levels of 200 or 400 mg. OS appeared to correlate with nimotuzumab dose, with the 3-year survival rate ranging from 16.7% for the 2 lower doses to 66.7% for the 2 higher doses (99). Based on serum levels, the nimotuzumab dose of 200 mg/wk was selected for further clinical testing. A phase IIb 4-arm open-label randomized study evaluated nimotuzumab 200 mg/wk $\times$ 6 weeks in combination with RT to a total dose of 66 Gy alone or RT to 66 Gy with concurrent fixed, low-dose weekly cisplatin at 50 mg/wk in patients with locally advanced (stage III or IV), inoperable SCCHN (100). Ninety-two patients were randomly assigned to receive a) RT alone, b) RT with nimotuzumab, c) RT/cisplatin, and d) RT/cisplatin plus nimotuzumab or without platinum and nimotuzumab. PFS and OS were significantly higher in the groups of patients who received nimotuzumab in comparison with the control arms without nimotuzumab, whereas toxicities were expected (100). Based on these results, additional clinical trials are ongoing and a phase III trial in the postoperative treatment setting is planned (see Table 6.3).

EGFR Tyrosine Kinase Inhibitors

EGFR-TKIs bind intracellularly to the ATP pocket of EGFR to competitively inhibit receptor activity and thereby block the downstream signaling pathways (101). EGFR-TKIs that have been studied in SCCHN include erlotinib, gefitinib, and lapatinib.

Erlotinib

Erlotinib is approved by the FDA for the second- or third-line treatment of non-small cell lung cancer as monotherapy and for the first-line treatment of pancreatic cancer in combination with gemcitabine. Erlotinib has moderate single-agent activity in recurrent or metastatic SCCHN. In a phase II

study, 115 patients with recurrent or metastatic SCCHN were treated with erlotinib 150 mg once-daily, orally. Five patients (4%) achieved a PR, and 44 patients (38%) had disease stabilization with a median duration of 16 weeks. The median PFS was approximately 2.2 months, and the median OS was 6.0 months (102). The combination of erlotinib with various chemotherapeutic agents has been evaluated in phase II clinical trials in recurrent or metastatic SCCHN (103,104).

Erlotinib was combined with docetaxel and RT in a phase I clinical trial in patients with previously untreated, locally advanced SCCHN (see Table 6.4). The regimen consisted of weekly docetaxel at doses 15 to 20 mg/m² plus erlotinib once daily, orally at escalating doses from 50 to 150 mg with concurrent RT to 70.2 Gy (1.8 Gy per fraction). Patients could receive maintenance treatment with erlotinib for up to 2 years. Three patients developed dose-limiting toxicities, 1 in each of the first 3 levels but no dose-limiting toxicity was observed on the 4th dose level. Preliminary efficacy data were very encouraging with 15 of 18 evaluable patients achieving a CR. No significant pharmacokinetic interaction of erlotinib with docetaxel was noted (105). Erlotinib at full dose (150 mg daily) and docetaxel (20 mg/m² weekly during RT) were the recommended doses for a follow-up phase II clinical trial that is currently ongoing (NCT00720304).

A phase II study evaluated the combination of erlotinib, cisplatin, and RT (70.2 Gy) in locally advanced SCCHN (see Table 6.4). Of a total of 31 patients, 21 (84%) had a pathologic CR, 2 had residual disease and underwent salvage surgery, and 1 patient progressed. Radiation dermatitis ($n = 14$), nausea ($n = 13$), mucositis ($n = 9$), and vomiting ($n = 8$) were the most common adverse events (106). The combination of erlotinib, cisplatin, and RT was tested in a phase I study in patients with surgically resected locally advanced SCCHN (107). Finally, erlotinib has been combined with bevacizumab and RT after IC (108). Several studies with erlotinib in patients with locally advanced SCCHN are currently ongoing (see Table 6.5).

TABLE 6.4
Phase I or II trials of gefitinib or erlotinib in locally advanced SCCN

Treatment Regimen	Patient Population	Primary End Point Sample Size	Main Findings/ Comments	Author/Reference
IC: paclitaxel, carboplatin CRT: RT plus 5-FU, hydroxyurea, and gefitinib Maintenance: gefitinib for 2 years	Previously untreated, stage IV: 91% 57% oropharynx	CR at the end of CRT, PFS (<i>n</i> = 67)	• Gefitinib at 250 mg/d • 56 pts evaluable for response • 51 CR (91%), 4 PR (7%), and 1 PD (2%) after CRT • Estimated PFS at 2 and 3 years: 77% and 64%, respectively • Estimated OS at 2 and 3 years: 83% and 77%, respectively • Grade 3/4 mucositis (85%), dermatitis (32%) • Median days on gefitinib: 667	Ahmed et al (115)
CRT: RT plus gefitinib (cohort A) and RT plus cisplatin and gefitinib (cohort B) Maintenance: gefitinib for 2 years	56% stage IV 65% oropharynx	Safety (<i>n</i> = 23)	• Cohort A: 8 pts • Cohort B: 15 pts • Grade 3/4 mucositis (57%), dysphagia (39%), neutropenia (30%), hyponatremia (30%), nausea/vomiting (22%) • No difference between the 2 doses of gefitinib (250 mg/d versus 500 mg/d) • Estimated 1-year LRC, DFS, and OS: 91%, 82%, and 87%, respectively	Chen et al (114)
CRT: RT plus paclitaxel and gefitinib	Stage III-IVB, previously untreated	Safety (<i>n</i> = 10)	• MTD: gefitinib (250 mg/d) and paclitaxel 36 mg/m²/weekly • Grade 3/4 mucositis (7 pts), interstitial pneumonitis (1 pt) • DLT: severe and prolonged mucositis	Morris et al (116)

CRT: RT plus cisplatin, 5-FU and gefitinib Maintenance: gefitinib for 2 years	Stage IV: 80%, previously untreated 68% oropharynx	OS, distant control (<i>n</i> = 60)	- Results were compared retrospectively to historical control without gefitinib - Transient renal dysfunction (28% versus 5%, <i>P</i> = 0.002) - Myelosuppression: similar with that of historical control 5 deaths during treatment with gefitinib versus 1 - Local control, 80% versus 88% - distant control, 86% versus 76% - OS, 67% versus 68%	Rodriguez et al (117)
IC: docetaxel, carboplatin, 5-FU plus gefitinib CRT: RT plus docetaxel weekly and gefitinib Maintenance: gefitinib	53% stage IV 55% oropharynx	Safety (<i>n</i> = 62)	- During IC: grade 3/4 mucositis (27%), diarrhea (16%), neutropenia (31%) - During CRT: grade 3/4 mucositis 55% - ORR after IC: 46% - PR after CRT 44%; CR after CRT 36% 2- and 3-year OS: 76% and 54%, respectively	Hainsworth et al (118)
CRT: RT plus docetaxel weekly and erlotinib Maintenance: erlotinib for 2 years	Stage IV: 87%, pharynx (<i>n</i> = 15),	Safety (<i>n</i> = 23)	- Docetaxel doses from 15 mg/m²–20 mg/m² and erlotinib 50–150 mg - One DLT in each of the first 3 levels 15/18 evaluable patients achieved CR - Recommended doses: docetaxel 20 mg/m² and erlotinib 150 mg/d	Savvides et al (105)
CRT: RT plus cisplatin every 3 weeks and erlotinib	Stage IV: 61% 42% oropharynx	Safety, ORR (<i>n</i> = 31)	- pCR: 23 pts (76.7%) - Grade 3/4 nausea (48%), in-field dermatitis (57%), dysphagia (35%), mucositis (29%), neutropenia (6%)	Herchenhorn et al (106)

CR, complete response; pCR, pathological complete response; PR, partial response; OS, overall survival; IC, induction chemotherapy; LRC, locoregional control; CRT, chemoradiotherapy; PFS, progression-free survival; DFS, disease-free survival; ORR, overall response rate; RT, radiotherapy; SCCHN, squamous cell carcinoma of the head and neck; PD, progressive disease; 5-FU, 5-fluorouracil; DLT, dose-limiting toxicity; MTD, maximum tolerated dose; pts, patients.

TABLE 6.5
Ongoing or recently completed trials of EGFR-TKIs in locally advanced SCC/HN

Regimen	Phase	Center/Sponsor	Primary End Point	ClinicalTrials.gov Identifier
ERLOTINIB				
Concurrent with RT: cisplatin plus erlotinib and bevacizumab	II	Duke University, Genentech, OSI Pharmaceuticals	CR	NCT00140556
Concurrent with RT: docetaxel/erlotinib	II	Case Comprehensive Cancer Center	PFS, TTP	NCT00720304
Concurrent with postoperative RT: cisplatin plus erlotinib	I/II	Grupo De investigacion, Clinica en Oncologica Radioterapia	Safety, PFS	NCT00442455
Concurrent with RT: intra-arterial cisplatin plus erlotinib	II	Southern Illinois University	ORR	NCT00304278
Maintenance: erlotinib	II	Geisinger Clinic, Genentech	DFS	NCT00750555
GEFITINIB				
Concurrent with postoperative RT: cisplatin versus cisplatin plus gefitinib (CARISSA)	II/III	Groupe Oncologie Radiotherapie Tete et Cou	Safety/Efficacy	NCT00169221
LAPATINIB				
IC: docetaxel, cisplatin, and 5-FU (TPF) Concurrent with RT: carboplatin plus lapatinib	I/II	European Organization for Research and Treatment of Cancer	Safety	NCT00498953
Concurrent with postoperative RT: platinum-based chemotherapy plus placebo versus platinum-based chemotherapy plus lapatinib	III	Multicenter (GlaxoSmithKline)	DFS	NCT00424255
Maintenance: placebo versus lapatinib				
Concurrent with RT: lapatinib	II	Stanford University	TTP	NCT00490061
Concurrent with RT: cisplatin versus cisplatin plus lapatinib	II/III	Multicenter (GlaxoSmithKline)	CR rate	NCT00387127

EGFR-TKIs, epidermal growth factor receptor-tyrosine kinase inhibitors; CR, complete response; RT, radiotherapy; PFS, progression-free survival; TTP, time-to-progression; ORR, overall response rate; DFS, disease-free survival; IC, induction chemotherapy.

Gefitinib

Gefitinib has modest single-agent activity in recurrent or metastatic SCCHN with RRs 1% to 11% (109–111). Two phase III randomized trials did not show survival benefit of single-agent gefitinib at doses of either 250 or 500 mg daily over standard methotrexate (112) or of docetaxel plus gefitinib versus docetaxel plus placebo in patients with recurrent or metastatic SCCHN (113).

The combination of gefitinib with CRT has shown an acceptable toxicity profile in phase I and II studies in locally advanced SCCHN (see Table 6.4) (114–118).

A phase I clinical trial evaluated the combination of escalating doses of gefitinib (250 or 500 mg/d) with RT or CRT (114). Eight patients received gefitinib concurrently with RT alone (cohort A), and 15 patients received the same regimen plus weekly cisplatin 30 mg/m² (cohort B). Patients also could receive gefitinib 250 mg as adjuvant therapy for up to 2 years. No dose-limiting toxicities were observed in cohort A. In cohort B, dose-limiting toxicities included 1 grade 4 diarrhea and 1 grade 4 neutropenic fever. Mucositis (57%), dysphagia (39%), neutropenia (30%), hyponatremia (30%), and nausea/vomiting (22%) were the most common adverse events. There were no significant differences in toxicities between the 2 doses of gefitinib. Fifteen patients of the 23 who were enrolled in the study received gefitinib as adjuvant therapy for a median time of 19 months (1–25.3 months). The clinical CR was 91% at the primary site and 82% at the neck. The estimated 1-year LRC, DFS, and OS were 91%, 82%, and 87%, respectively (114). In another phase I study, gefitinib was added to weekly paclitaxel and concurrent RT in patients with treatment-naïve locally advanced SCCHN. The MTD was gefitinib 250 mg daily and paclitaxel 36 mg/m². The most common toxicity was mucositis. Five patients had a CR and 1 a PR (116). The integration of gefitinib into a nonplatinum-containing concurrent CRT regimen was tested in a phase II study. Sixty-seven patients received 2 cycles of IC with paclitaxel and carboplatin followed by concurrent RT

with 5-FU, hydroxyurea, and gefitinib 250 mg daily. The regimen was highly efficacious. Of 56 evaluable patients, 51 (91%) achieved a CR after completion of CRT. The estimated 2- and 3-year PFS was 77% and 64%, respectively, and the 2- and 3-year OS was 83% and 73%, respectively. The incidence of grade 3/4 mucositis was very high in this study (75%/10%). Grade 3 and 4 dermatitis was seen in 29% and 3% of patients, respectively, whereas rash and diarrhea were rare (115).

Another phase II trial evaluated gefitinib, concurrently with cisplatin, 5-FU, and RT (117). Acute toxicities, including transient renal dysfunction and hospital admissions were significantly increased with the addition of gefitinib compared to a historical control without gefitinib. However, efficacy parameters were not improved with gefitinib (117).

Finally, the addition of gefitinib to IC and subsequent CRT was evaluated in a phase II clinical trial (118). Sixty-two patients with locally advanced SCCHN (53% stage IV and 55% with oropharyngeal primary) were treated with a 6-week IC regimen with docetaxel 60 mg/m² and carboplatin AUC 5 every 3 weeks plus daily infusional 5-FU 200 mg/m² and oral gefitinib 250 mg that was followed by RT to a total dose of 68.4 Gy with concurrent weekly docetaxel 20 mg/m² and daily gefitinib 250 mg/d. Patients received gefitinib for up to 2 years. The gefitinib-containing induction regimen resulted in considerable grade 3 mucositis (27%) and grade 3 diarrhea (16%), while during CRT, 59% of patients experienced grade 3 or 4 mucositis or dysphagia. Only 27% of patients completed the full infusional 5-FU course during induction as planned. The RR after induction and CRT in evaluable patients was 46% and 80%, respectively, including CR rates of 14% and 36%, respectively. With a median follow-up of 33 months, the estimated 3-year PFS and OS rates were 41% and 54%, respectively, which do not appear superior to survival results reported with CRT alone (118). Ongoing trials with gefitinib are included in Table 6.5.

Lapatinib

Lapatinib is a dual-kinase inhibitor that targets both EGFR and HER-2 and may inhibit their dimerization. As a single agent, lapatinib was well tolerated but produced no objective responses in a phase II study in recurrent or metastatic SCCHN (119). In preclinical models, lapatinib has synergistic activity with chemotherapy and RT (120). In a phase I clinical trial the combination of lapatinib with RT and cisplatin was evaluated. Thirty-one patients were treated with RT, cisplatin, and escalating doses of lapatinib (500, 1000, and 1500 mg). No DLTs were observed, and the recommended phase II dose of lapatinib was 1500 mg daily. Radiation dermatitis, mucositis, lymphopenia, and neutropenia were the most common side effects. The ORR was 81% (121). Lapatinib was also combined with TPF (cisplatin 75 mg/m², docetaxel 60 mg/m² for the first cycle, then 75 mg/m², and 5-FU 750 mg/m² as CI for 5 days, administered every 3 weeks) as IC for patients with locally advanced larynx and hypopharynx SCC. However, this combination regimen was associated with unacceptable toxicities, predominantly renal failure, even at the lower lapatinib dose of 500 mg/d that led the investigators not to recommend it for further use (122). Currently, lapatinib is under investigation in a number of trials, including a phase III trial in high-risk resected SCCHN (NCT00424255) (see Table 6.5).

■ PREDICTORS OF OUTCOME AFTER TREATMENT WITH EGFR INHIBITORS

EGFR protein expression has not been correlated with clinical outcome after treatment with EGFR inhibitors (123–125). An ECOG trial in recurrent or metastatic SCCHN that compared cisplatin with or without cetuximab reported a higher RR with the addition of cetuximab to cisplatin in patients with tumors with lower to moderate EGFR protein expression but similar RRs in patients with tumors with high EGFR expression (126). A possible explanation suggested by the

authors was that the dose of cetuximab was not sufficient to saturate the number of receptors in tumors with high EGFR expression. Although EGFR gene copy number has been associated with poor prognosis in patients with SCCHN (127–129), it was not predictive of efficacy for cetuximab-based treatment in recurrent or metastatic SCCHN (130).

EGFR can activate multiple redundant signaling pathways resulting in survival and proliferation of tumor cells. Alterations downstream of EGFR or cross talk with other receptors and pathways can potentially promote tumor growth independently of EGFR-blockade (123,131–133). High levels of vascular endothelial growth factor (VEGF) and interleukin-6 (IL-6) in the serum have been suggested as predictive markers of poor response to cetuximab-based therapy (134). EGFR mutations have been associated with a dramatic response to EGFR-TKIs in patients with non-small cell lung cancer; however, these mutations are exceedingly rare in SCCHN, ranging between 0% and 7.5% (127,128,135,136). EGFRvIII is a mutant form of EGFR described mainly in glioblastomas that was also detected in 42% of SCCHN in 1 study (137). EGFRvIII results in ligand-independent activation of the receptor and has been proposed as a mechanism of resistance to wild-type EGFR targeting with cetuximab. Furthermore, matrix-assisted laser desorption ionization mass spectrometry has been used to evaluate serum profiles that are potentially predictive of the survival of patients with recurrent or metastatic SCCHN treated with either EGFR-TKIs or cetuximab (138).

Skin toxicity, mainly acneiform rash, is the most common adverse event associated with anti-EGFR agents that occurs in approximately two-thirds of patients, usually in the first 3 weeks of treatment and it is probably related to EGFR expression in the skin (139). Several studies in solid tumors, including SCCHN, have shown a direct correlation between the development of rash and better patient outcome after EGFR inhibitor therapy (102,109,124,126,140).

Vascular-targeted Therapies

Tumor cells secrete pro-angiogenic growth factors that mediate the process of angiogenesis. VEGF, which is a key angiogenic factor, and its receptor (vascular endothelial growth factor receptor [VEGFR]) are upregulated in many neoplasms, including SCCHN (141–144). In a recent meta-analysis of 12 studies in SCCHN, VEGF expression was correlated with a 1.88-fold higher risk of death at 2 years (145). Several studies have shown that the use of antiangiogenic agents leads to a significant inhibition of tumor growth, including that of SCCHN (146, 147).

Vascular-targeted therapies include a) antiangiogenic agents that inhibit the formation of new vessels that include VEGF ligand-targeted moAbs (e.g., bevacizumab) and small-molecule inhibitors of VEGFR, which are oral drugs that inhibit the intracellular tyrosine kinase activity of VEGFR, and b) vascular-disrupting agents (VDAs) that target mature tumor blood vessels, leading to ischemia and necrosis. VDAs destabilize microtubules and selectively disrupt immature tumor endothelial cells, resulting in the discontinuation of blood flow and eventually, cell death.

Antiangiogenic factors have been correlated with certain severe adverse events, including bleeding, colon perforation, hypertension, and proteinuria. Bevacizumab is contraindicated in patients with squamous cell carcinoma of the lung due to the high risk of fatal hemoptysis. Bevacizumab, especially in combination with RT, has been generally safe in patients with SCCHN, even though serious or even fatal bleeding events have been reported. A causal relationship of bleeding to antiangiogenesis agents is often difficult to establish in nonrandomized, single-arm trials since bleeding events are rather common in the natural history of SCCHN, especially with recurrent or previously irradiated tumors. Attention should also be paid to the risk of other thrombosis and other acute or late complications that may ultimately determine the therapeutic index of these agents in the curative treatment setting (148).

Anti-VEGF therapy seems to increase blood flow in the environment of tumor and therefore the delivery of oxygen and of anticancer therapy (149). Preclinical and clinical studies have shown that these agents can potentiate chemotherapy and RT efficacy (150–153).

Antiangiogenic Agents

Monoclonal Antibodies

Bevacizumab

Bevacizumab is a fully humanized monoclonal antibody that binds VEGF-A. It has been approved for the treatment of several advanced solid tumors, including colorectal cancer, renal cancer, breast cancer, nonsquamous non-small cell lung cancer, and glioblastomas. The mechanism of action of bevacizumab is thought to be through angiogenesis inhibition as well as by facilitation of delivery of chemotherapeutic agents by decreasing microvascular permeability and decreasing intratumoral pressure (154,155), which may explain why bevacizumab acts synergistically with cytotoxic or other targeted agents. University of Pittsburgh investigators have presented encouraging preliminary efficacy results with pemetrexed plus bevacizumab in the first-line treatment of recurrent or metastatic SCCHN (NCT00222729). However, bleeding complications were also seen (57). The addition of bevacizumab to a cisplatin doublet (PF or cisplatin/docetaxel) is being tested in an ongoing phase III trial in recurrent or metastatic SCCHN (NCT00588770).

VEGF signaling is upregulated by EGFR expression (156). EGFR signaling induces VEGF expression and angiogenesis (157), whereas targeting EGFR leads to the inhibition of VEGF secretion by tumor cells and, thus, to antiangiogenic activity (158–162). Therefore, the combination of EGFR and VEGF/VEGFR inhibitors has attracted the interest of clinical investigators. A phase I/II trial evaluated the combination of bevacizumab in escalating dose levels up to 15 mg/kg every 3 weeks and erlotinib 150 mg daily

in patients with recurrent or metastatic SCCHN. Although there were no DLTs, 3 serious bleeding events occurred, 1 of which was fatal. Efficacy results were promising. In the phase II part of the study, 4 of 48 patients (8%) had a CR and 3 a PR (6%) and 26 stable disease (SD) (56%). Median PFS and OS were 4.1 and 7.1 months, respectively (163). The combination of cetuximab and bevacizumab is also being studied with promising preliminary antitumor activity and rare bleeding complications in a phase II multicenter trial (NCT00409565) (164). Preclinical data have supported the combination of bevacizumab and an EGFR inhibitor with concurrent radiation (165). The concept of building on cetuximab-containing CRT by adding bevacizumab is currently being evaluated in a randomized phase II trial of pemetrexed, cetuximab, and RT plus or minus bevacizumab that is conducted at the University of Pittsburgh (NCT 00703976) and a phase II trial of cisplatin, cetuximab, bevacizumab, and RT at Memorial Sloan-Kettering Cancer Center (NCT00968435) (see Table 6.6).

Contrary to initial theoretical concerns that inhibition of angiogenesis could increase tumor hypoxia leading to radioresistance (166), preclinical studies have shown that antiangiogenic agents improve the blood flow and oxygenation of tumors and radiosensitivity (167–170).

Currently, the addition of bevacizumab to CRT regimens is being investigated in multiple clinical

trials in locally advanced SCCHN (see Table 6.7). Two studies from the University of Chicago have added bevacizumab to a nonplatinum regimen of hydroxyurea, 5-FU, and RT (FHX). In a phase I study, 43 patients with recurrent, previously irradiated or poor-prognosis, treatment-naïve SCCHN were treated with bevacizumab administered in escalating doses from 2.5 to 10 mg/kg every 2 weeks, hydroxyurea 500–1000 mg twice daily, and 5-FU 600–800 mg/m² as a continuous infusion for 5 days in combination with RT (1.8–2 Gy once daily) on a week on-week off schedule (171). The MTD of bevacizumab was 10 mg/kg in combination with 5-FU 600 mg/m² and hydroxyurea 500 mg; this cohort was expanded to 26 patients. A total of 43 patients were enrolled in this study. The median OS for reirradiated patients with recurrent, non-metastatic disease was 10.3 months. Severe late toxicities were significant: 5 patients developed a fistula and 4 patients developed ulceration or tissue necrosis for which surgical reconstruction was required. Furthermore, 3 patients developed thrombosis, 1 patient had a fatal carotid blowout, and 1 patient had a fatal esophageal bleed. The high incidence of complications observed in this study may be related to the selection of patient population. Although some of the adverse events were likely related to bevacizumab, their frequency may not be higher compared with reports from other reirradiation studies. The incidence of fistula and tissue necrosis will require careful monitoring in future clinical

TABLE 6.6
Ongoing phase II trials of cetuximab plus bevacizumab in locally advanced SCCHN

Regimen	Phase	Center	Primary End Point	ClinicalTrials.gov Identifier
Concurrent with RT: Pemetrexed and cetuximab with or without bevacizumab	IIR	University of Pittsburgh	PFS	NCT00703976
Concurrent with RT: cisplatin, cetuximab, and bevacizumab	II	Memorial Sloan-Kettering Cancer Center	PFS	NCT00968435

PFS, progression-free survival; RT, radiotherapy.

trials of bevacizumab in treatment-naïve patients with SCCHN. In a subsequent phase II randomized study, the University of Chicago group investigated the combination of 5-FU (600 mg/m²/d continuous infusion for 5 days) and hydroxyurea (500 mg orally twice daily) with or without bevacizumab (10 mg/kg every 2 weeks) concurrently with twice daily RT on a week on-week off schedule in patients with intermediate-stage (predominantly excluding N2-N3) SCCHN. A preliminary report from the first 24 patients enrolled in this study showed that the incidence of mucositis and dermatitis was not increased with the addition of bevacizumab to CRT. However, there was an increase in neutropenia and vascular complications in the bevacizumab arm. Efficacy results were not mature at the time of presentation, but there was a concern for a lower efficacy in T4 primary tumors with bevacizumab plus FHX (172) (see Table 6.7). The RTOG recently completed a phase II trial of bevacizumab, cisplatin, and RT followed by adjuvant bevacizumab, cisplatin, and 5-FU in patients with locally advanced nasopharyngeal carcinoma (NCT00408694). Results of this study are not yet available.

The combination of RT (70.2 Gy total; 1.8 Gy/day) with docetaxel (20 mg/m² weekly) and bevacizumab (5 mg/kg every 2 weeks and for up to 1 year after RT) was feasible as shown by preliminary results of a phase II clinical trial (NCT00281840) (173) (see Table 6.7). Another phase II study investigated the addition of bevacizumab (15 mg/kg on days 1, 21, and 43) to cisplatin (50 mg/m² on days 1, 2, 22, 23, 43, and 44) and RT (70 Gy) (174). Although this study was originally designed to include maintenance bevacizumab for 6 months, this part of the treatment was discontinued after the occurrence of a grade 4 pulmonary hemorrhage. Functional mucositis of grade 3 occurred in 76% of patients. Two patients died within 90 days of last treatment; one had a sudden death and another died from aspiration pneumonia. Efficacy results were promising but not mature at the time of presentation (174) (see Table 6.7).

Bevacizumab has also been incorporated into IC regimens (see Table 6.7). In a phase II

study, 60 patients with locally advanced SCCHN received 2 cycles of IC with paclitaxel, carboplatin, and 5-FU plus bevacizumab followed by concurrent RT with paclitaxel, bevacizumab, and erlotinib (108). Preliminary results showed that 94% of patients completed the induction part of the treatment and 85% all therapy. The most common grade 3 or 4 adverse events during IC were neutropenia (46%), neutropenic fever (6%), mucositis (14%), and diarrhea (14%); a high rate of grade 3 or 4 mucositis of 76% was observed during CRT. An ORR of 77% after completion of the entire treatment was reported (108).

Vascular Endothelial Growth Factor Receptor Tyrosine Kinase Inhibitors *Sorafenib*

Sorafenib is an oral small-molecule multikinase inhibitor of VEGFR2, VEGFR3, platelet-derived growth factor receptor (PDGFR) β , RET, c-Kit, and Raf-1, which has been approved by the FDA for the treatment of metastatic renal cell carcinoma and unresectable hepatocellular carcinoma. Sorafenib at a dose of 400 mg twice daily has been evaluated in 2 phase II studies, one conducted by SWOG and another by a Canadian group, in patients with recurrent or metastatic SCCHN. These studies that differed somewhat in eligibility criteria (prior chemotherapy was allowed in the Canadian study) demonstrated low or modest single-agent activity for sorafenib with RR 4% to 5%, median PFS of 1.8–4 months, and median survival of 4–9 months (175). Toxicities were expected and there were no bleeding episodes, whereas a case of grade 4 pulmonary embolism was reported in the SWOG study (176). Another monotherapy sorafenib study is ongoing (NCT00199160). Sorafenib is also being tested in combination with cetuximab (NCT00939627, NCT00815295) as well in combination with carboplatin and paclitaxel (NCT00494182) in patients with recurrent or metastatic SCCHN. Finally, sorafenib was studied in combination with cisplatin and RT in a phase I trial in patients with locally advanced SCCHN (NCT00627835).

TABLE 6.7
Phase II clinical trials of bevacizumab in locally advanced SCC HN

Treatment Regimen	Patient Population	Primary End Point/Sample Size	Main Findings	Author/Reference
IC: paclitaxel, carboplatin, 5-FU and bevacizumab Concurrent with RT: paclitaxel, bevacizumab, erlotinib	T3-T4 or N1-3	PFS ($n = 60$)	• 48 pts included in this preliminary report • 45 pts (94%) completed IC and 41 pts (85%) completed CRT • ORR: 56% after IC and 77% after CRT • 18-month PFS and OS: 85% and 87% • Grade 3/4 toxicities during IC: neutropenia (46%), mucositis (14%), diarrhea (14%), neutropenic fever (6%); grade 3/4 toxicity during CRT: mucositis (76%)	Meluch et al (108)
Concurrent with RT: docetaxel plus bevacizumab	100% stage (preliminary report) 67% pharynx,	TTP ($n = 30$)	• 12 included in the preliminary report, 10 evaluable • 9 pts CR, 1 pt PD • 6/10 pts underwent neck dissection and all had pCR • 1 pt had hemorrhagic cholecystitis	Savvides et al (173)

Concurrent with RT: cisplatin plus bevacizumab	93% oropharynx	PFS ($n = 42$)	• LRC: 100% • 3 pts developed distant metastasis • Estimated 1-year PFS and OS: 83% and 88% • Grade 3/4 toxicities: mucositis (76%), nausea (24%) and neutropenia (31%) • 2 deaths within 90 days of last treatment (1 aspiration pneumonia, 1 sudden death)	Pfister et al (174)
Concurrent with RT: 5-FU, hydroxyurea (FHX) versus 5-FU, hydroxyurea, bevacizumab (B-FHX) Phase II randomized study	“Intermediate stage” (T2-3N0-1 or T4N0-1)	PFS Planned sample size, $n = 72$ (2:1 randomization)	• Preliminary safety report on 24 pts evaluable for toxicity (FHX, 8 pts; B-FHX 16 pts) • Mucositis grade 3–4 (FHX vs B-FHX): 75% vs 81% and dermatitis grade 2/3 (FHX vs B-FHX): 75% vs 38% • 6 deaths occurred, all in B-FHX (relapse, 2; infection, 3; unknown, 2) • Clinical response in 21 pts • FHX- 4 CR; 4 PR • B-FHX- 6 CR; 7 PR	Choong et al (172)

CR, complete response; PR, partial response; OS, overall survival; IC, induction chemotherapy; LRC, locoregional control; CRT, chemoradiotherapy; PFS, progression-free survival; RR, response rate; RT, radiotherapy; SCCHN, squamous cell carcinoma of the head and neck; TTP, time-to-progression; PD, progressive disease; 5-FU, 5-fluorouracil; pts, patients.

Sunitinib

Sunitinib is a small-molecule TKI of VEGFR1, VEGFR2, VEGFR3, PDGFR α and β , colony-stimulating factor-1 receptor, c-Kit, and Flt-3. It has been approved by the FDA for the treatment of renal cell carcinoma. The combination of sunitinib, cetuximab, and radiation was evaluated in an orthotopic head and neck cancer model. Concomitant administration of the drugs produced a marked and significant supra-additive decrease, while the addition of RT led to complete inhibition of the tumor growth (177). Sunitinib has been tested as monotherapy in 3 phase II studies in recurrent or metastatic SCCHN (178–180). These studies demonstrated that single-agent sunitinib has modest activity with ORR less than 10% in recurrent or metastatic SCCHN. Moreover, there has been a concern that sunitinib is associated with a high risk for bleeding events. In 1 of these studies 4 patients out of the 37 who enrolled died from bleeding possibly related to sunitinib (178). Although sunitinib cannot be recommended for further testing as monotherapy, it is being studied in combination with cetuximab and RT (NCT00906360).

Semaxanib

Semaxanib (SU5416) inhibits the tyrosine kinase of VEGFR2. In a phase II study, 35 patients with recurrent or metastatic SCCHN were treated with semaxanib administered intravenously at 145 mg/m² twice per week, for 8 consecutive weeks. One PR and 1 minor response were reported. The median OS was 6.2 months. However, 31% of patients experienced grade 3 headache, and 1 patient suffered fatal carotid artery hemorrhage (181). This agent did not show promising results in solid tumors, and its development has been discontinued.

Cediranib

Cediranib (AZD2171) is an oral highly potent and selective TKI of all VEGF receptors. In SCCHN xenograft models, the combination of gefitinib, cediranib, and RT showed synergistic effects.

Currently, this agent is being tested as monotherapy in a phase II clinical trial in recurrent or metastatic SCCHN (NCT00458978).

Vandetanib

Vandetanib (ZD6474) is an oral small-molecule TKI of VEGFR2, EGFR, and RET. It is highly active in SCCHN cell lines and xenografts (182). Vandetanib also showed synergistic effect when it was administered in combination with radiation in SCCHN xenografts (183). Preliminary results from an ongoing phase I study of cisplatin/RT plus vandetanib or vandetanib/RT were recently reported. The MTD of vandetanib was 100 mg/d for the CRT regimen, and the investigators continue to accrue patients at the MTD (184). Vandetanib is being studied in a phase II randomized trial in combination with cisplatin and RT in high-risk resected SCCHN (RTOG 0619; NCT00720083).

Vatalanib

Vatalanib (PTK/ZK) is a small-molecule TKI of all VEGF receptors (more selective for VEGFR2), PDGFR, and c-Kit. Its antitumor and antiangiogenic activities have been examined in preclinical studies (185–187) and in several clinical trials for cancers such as CRC and thyroid cancer (186,188–191). PTK/ZK inhibited the phosphorylation of VEGFR2 in endothelial cells and decreased the microvessel density of SCCHN xenografts (192). A recent study demonstrated that PTK/ZK blocks downstream targets of VEGF signaling in endothelial cells and suggested that this drug may inhibit the angiogenic switch in SCCHN (193).

Vascular-disrupting Agents

VDA target established tumor blood vessels that results in tumor ischemia and necrosis. In comparison with anti VEGF/VEGFR agents, VDAs may have a faster onset of antitumor effect (71). ZD6126 is a VDA that has been investigated in an SCCHN xenograft model. Although when

administered alone this agent had limited antitumor activity, in combination with an anti-EGFR agent (gefitinib) it showed supra-additive antitumor effect. However, when the ZD6126/gefitinib regimen was combined with radiation, no additional benefit was observed (194). Another VDA tested in xenograft models of SCCHN is DMXAA (ASA404) (195). This class of agents is worthwhile to investigate in combination with chemotherapy or RT in SCCHN.

Src Family Kinase Inhibitors

The Src family of nonreceptor protein kinases includes 8 members (c-Src, C-Yes, Fyn, Blk, Fgr, Hck, Lck, and Lyn) of which c-Src is more often implicated in cancer (63). Although c-Src is rarely mutated, it is usually overexpressed and/or activated in many solid tumors, including SCCHN (196,197). Src family kinases have been implicated in tumor invasion, changes in adhesion, cell motility, and migration and can mediate the signaling of a number of receptors including growth factor receptors, integrins, and cytokine receptors.

Dasatinib and AZD0530 are oral multikinase inhibitors that inhibit Src family kinases that undergo clinical testing in hematologic malignancies and solid tumors. Dasatinib is a potent inhibitor of multiple oncogenic kinases, including BCR-ABL, Src, c-Kit, PDGFR, and others (198). Because of its ability to inhibit BCR-ABL, dasatinib was developed and approved by the FDA for the treatment of chronic myelogenous leukemia. Dasatinib is also being tested in phase I and II clinical trials in solid tumors. Preclinical studies have shown that dasatinib suppresses invasion and induces cell cycle arrest and apoptosis in SCCHN cell lines (199). Investigators at the MD Anderson Cancer Center conducted a phase II study with single-agent dasatinib (100 mg twice daily) in patients with previously treated, recurrent or metastatic SCCHN (NCT00507767). Toxicity was acceptable but the efficacy end point of the study was not met since no objective response was

observed in 13 evaluable patients (200). Dasatinib is being evaluated in combination with cetuximab and RT with or without cisplatin in patients with locally advanced SCCHN (NCT00882583). AZD0530 is a more selective inhibitor of c-Src and ABL (201). This agent is also being studied in recurrent or metastatic SCCHN (NCT00513435).

Combined targeting of Src and EGFR pathways is supported by preclinical data (63,202). Src kinases have been shown to potentiate EGFR signaling (203). EGFR activation leads to Src kinase activation, while treatment with EGFR inhibitors in vitro results in reduced activity of c-Src (63). Combined treatment with AZD0530 and gefitinib resulted in greater inhibition of growth and invasion of SCCHN cells compared with either agent alone (202). Furthermore, dasatinib in combination with cetuximab has been tested in colon cancer cell lines resistant to dasatinib and was found to have synergistic growth inhibitory effects (204). At the University of Pittsburgh, we completed a phase I trial of cetuximab plus dasatinib in patients with various advanced solid malignancies (205). Dasatinib at a dose of 150 mg once daily was safely combined with a standard weekly cetuximab. Early-onset headache in cycle 1 was common and occasionally severe but was ameliorated when dasatinib was started 3 days after the loading dose of cetuximab. Other expected side effects of dasatinib, including pleural effusions, were seen. Our group plans a phase II trial of cetuximab and dasatinib in patients with recurrent or metastatic SCCHN.

Insulin-like Growth Factor Receptor Antibodies

A newly emerging target for cancer therapy is the insulin-like growth factor (IGF) signaling axis. Both clinical and preclinical studies have shown that insulin-like growth factor type I receptor (IGF-IR) and its ligands IGF-I and IGF-II are involved in the development and progression of numerous human cancers and in their metastatic potential (206–208). It has been shown that

IGF-IR is increased in human SCCHN and that it influences the proliferation and motility, with over-expression associated with poor prognosis (209). Moreover, IGF-IR and EGFR functionally heterodimerize in this disease (209). The combination of EGFR and IGF-IR inhibitors has produced promising preclinical data (209). Further exploration of targeting IGF-IR and its combination with anti-EGFR agents is warranted. A phase II study with IMC-A12 alone or in combination with cetuximab is ongoing in patients with recurrent or metastatic SCCHN (NCT00617734). Clinical studies combining cetuximab/RT plus IMC-A12 are planned.

Proteasome Inhibitors

The activation of nuclear factor- κ B (NF- κ B) and activator protein-1 (AP-1) signal transduction pathways have been identified as prominent events promoting tumor progression of hematopoietic and solid malignancies, including SCCHN (210–213). Targeting these factors or upstream signal transduction pathways by genetic or chemical inhibitors has been shown to effectively suppress the tumor phenotype *in vitro* as well as to inhibit tumor growth in animal models and the clinic (210,212,214–216).

The proteasome is a multicatalytic proteinase complex with a main function to degrade unneeded or damaged proteins by ubiquitination and proteolysis. Proteasomes are part of a major mechanism by which cells regulate the concentration of particular proteins and degrade misfolded proteins. The activated proteasome leads to the activation of NF- κ B and degradation of components of AP-1 and other signal pathways involved in the pathogenesis of cancer. The proteasome consists of a complex that mediates the turnover of many intracellular proteins, including those controlling cell signaling, survival, and cell cycle regulation.

Bortezomib (PS-341) is a selective inhibitor of the proteasome. Bortezomib has shown activity against different types of cancer cells (217–220)

and in animal models (221,222). It is currently approved for the treatment of recurrent multiple myeloma and mantle cell lymphoma. The molecular and clinical efficacy of bortezomib is more evident in hematologic malignancies and to a lesser extent in solid tumors (221–223). Combinations of bortezomib with other antineoplastic agents have been investigated in an attempt to increase antitumor effect. In an ongoing phase I trial, 17 patients with advanced or previously irradiated SCCHN were treated with RT with concurrent weekly cisplatin 30 mg/m² and escalating doses of bortezomib on 3 dose levels (0.7, 1.0, and 1.3 mg/m²) administered intravenously on days 1, 4, 8, and 11 of a 21-day cycle (224). No DLT occurred in the first 2 levels, while at the third level a patient developed grade 4 thrombocytopenia. Additional patients are enrolled at a bortezomib dose of 1.3 mg/m² (224).

A phase II ECOG study investigated bortezomib with or without irinotecan in patients with recurrent or metastatic SCCHN (225). Bortezomib alone was well tolerated, but the combination of bortezomib with irinotecan required a dose reduction for irinotecan; both regimens had relatively low efficacy (225). A phase I study of bortezomib, cetuximab, and RT with or without cisplatin in stage IV SCCHN patients has started (NCT00629226). Furthermore, a phase II study with docetaxel and bortezomib is currently recruiting patients with recurrent or metastatic SCCHN as well (NCT00425750).

Mammalian Target of Rapamycin (mTOR) Inhibitors

The mTOR is a serine-threonine kinase that participates in the regulation of cell growth, proliferation, and apoptosis through modulation of cell cycle progression. In SCCHN xenografts, mTOR blockade inhibits DNA synthesis, induces apoptosis, and results in tumor regression (226,227). Several studies with the mTOR inhibitor everolimus (or RAD001) are currently ongoing. These studies include the

combination of everolimus with erlotinib in recurrent or metastatic SCCHN (NCT00942734) and the combination of everolimus, cisplatin, and RT in the postoperative treatment setting (NCT00858663). Finally, a study with induction therapy with everolimus added to docetaxel and cisplatin is currently recruiting patients with locally advanced SCCHN (NCT00935961).

Histone Deacetylase Inhibitors

Epigenetic regulation by acetylation and deacetylation of histones plays a major role in the regulation of gene expression. Histone deacetylase (HDAC) inhibitors are a novel class of anticancer agents that result in hyperacetylation of histones, and thus render the DNA more open for transcriptional activity, resulting in expression of several genes that are otherwise silenced in cancer, such as the tumor suppressor genes (228,229). The exact mechanism by which HDACs exert their antitumor effect is not completely understood (230). Anticancer effects of HDAC inhibitors are also mediated through changes in acetylation of nonhistone proteins (e.g., HSP90, p53, HIF-1 α , α -tubulin). HDAC inhibitors can induce p21 (WAF1) expression, a regulator of p53 tumor suppressor activity and key mediator of G1 arrest and differentiation, and are involved in retinoblastoma protein (pRb)-dependent pathways (231). HDAC inhibitors have been shown to induce differentiation, cell cycle arrest, or apoptosis in tumor cells and to inhibit the growth of tumors in several animal models.

Vorinostat (SAHA), an oral hydroxamic derivative that inhibits class I and II HDACs, is the first HDAC inhibitor that was approved for cancer therapy (for cutaneous T-cell lymphoma). Vorinostat 400 mg once daily was generally well tolerated; grade 3–4 toxicities included thrombocytopenia ($n = 3$), anorexia ($n = 2$), and dehydration ($n = 2$) but did not produce any objective responses in 12 patients with recurrent or metastatic SCCHN (232). Panobinostat (LBH589),

another oral HDAC inhibitor, is under investigation in cutaneous T cell lymphoma as well as solid tumors. A phase I study is evaluating panobinostat (LBH589) in combination with RT for prostate, esophageal, and head and neck cancers (NCT00670553).

■ CONCLUSIONS AND FUTURE PERSPECTIVES

Treatment results for locally advanced SCCHN are likely to be improved by the integration of novel, molecularly targeted agents (Table 6.8). Currently, there is proof of principle for the use of anti-EGFR moAbs in SCCHN. Cetuximab is the first and only targeted agent for SCCHN to obtain regulatory approval in the United States and in other countries. The use of RT plus cetuximab in locally advanced SCCHN is usually reserved as an alternative to CRT, especially in patients who are not good candidates to receive cisplatin. An important subject of clinical investigations has been the addition of cetuximab to IC and/or CRT. The results of a recently completed phase III trial (RTOG 0522) that investigates the addition of cetuximab to accelerated boost RT with concurrent cisplatin are eagerly awaited and may define a new standard regimen for the treatment of locally advanced SCCHN. Many other EGFR inhibitors are in various stages of development. Monoclonal antibodies against EGFR, such as nimotuzumab, have produced promising results in phase II trials. However, it remains unclear whether a new anti-EGFR monoclonal antibody or an EGFR-TKI will be preferable to cetuximab. There are rapidly accumulated data for the potential role of vascular-targeting agents in SCCHN. Although antiangiogenic agents may have low single-agent activity in SCCHN, strategies for combination therapy, especially with bevacizumab, appear promising but require confirmation in phase III clinical trials. Finally, even though cisplatin has been the backbone of CRT regimens, pemetrexed shows promise in early clinical trials and may

TABLE 6.8

Selected targeted agents in development

Agent	Pharmaceutical Company	Mechanism of Action	Toxicity Profile	Phase of Development (head and neck cancer)
EPIDERMAL GROWTH FACTOR RECEPTOR INHIBITORS				
Cetuximab (Erbix, C225)	ImClone, Bristol-Myers Squibb, Merck KGaA	IgG1 chimeric anti-EGFR monoclonal antibody	• Rash • Infusion-related reactions • Hypomagnesemia	III
Panitumumab (Vectibix, ABX-EGF)	Amgen	IgG2 human anti-EGFR monoclonal antibody	• Rash • Infusion-related reactions • Hypomagnesemia	III
Zalutumumab (2F8, HuMax-EGFr)	Genmab	IgG1 human anti-EGFR monoclonal antibody	• Rash • Infusion-related reactions	III
Nimotuzumab (hR3, BIOMab EGFR, Theracim, Theraloc)	YM Biosciences (and other partners)	IgG1 humanized anti-EGFR monoclonal antibody	• Infusion-related reactions	III
Erlotinib (Tarceva, OSI-774)	Genentech, OSI Pharmaceuticals, Roche	EGFR-tyrosine kinase inhibitor	• Rash • Diarrhea	II
Gefitinib (Iressa, ZD1839)	AstraZeneca	EGFR-tyrosine kinase inhibitor	• Rash • Diarrhea	II
Lapatinib (Tykerb/Tyverb, GW-572016)	GlaxoSmithKline	EGFR and HER-2 tyrosine kinase inhibitor	• Rash • Diarrhea	III
ANTIANGIOGENESIS AGENTS				
Bevacizumab (Avastin)	Genentech/Roche	IgG1 humanized anti-VEGF-A monoclonal antibody	• Bleeding, thrombosis • Hypertension • Proteinuria	III

Sorafenib (Nexavar, BAY 43-9006)	Bayer	Multi-kinase inhibitor of VEGFR-2, VEGFR-3, PDG FR β , RET, c-Kit, Raf	• Rash/hand-foot syndrome • Diarrhea • Bleeding • Hypertension • Stomatitis	II
Sunitinib (Sutent, SU11248)	Pfizer	Multi-kinase inhibitor of VEGFR-1, VEGFR-2, VEGFR-3, PDGFR α and β , c-Kit, CSF-1R, Flt-3	• Rash • Hand-foot syndrome • Diarrhea • Bleeding, thrombosis • Hypertension • Stomatitis • Thrombocytopenia	II
Cediranib (Recentin, AZD2171)	AstraZeneca	VEGFR-1, -2, and -3 tyrosine kinase inhibitor	• Bleeding, thrombosis • Hypertension • Proteinuria • Rash • Diarrhea	II
Vandetanib (Zactima, ZD6474)	AstraZeneca	VEGFR-2, EGFR and RET tyrosine kinase inhibitor	• Rash • Diarrhea • Bleeding, thrombosis • Hypertension • Proteinuria • QTc prolongation	II
Varalanib (PTK787, PTK/ZK)	Bayer Schering, Novartis	Multi-kinase inhibitor of VEGFR-1 and -2, PDGFR β , c-Kit	• Bleeding, thrombosis • Hypertension • Proteinuria • Rash • Diarrhea	II

(continued)

TABLE 6.8 Continued

Agent	Pharmaceutical Company	Mechanism of Action	Toxicity Profile	Phase of Development (head and neck cancer)
SRC INHIBITORS				
Dasatinib (Sprycel, BMS-354825)	Bristol-Myers Squibb	Multi-kinase inhibitor of BCR-ABL, c-Kit, Src family, PDGFR, Eph receptors	• Pleural effusion • Headache • Hypophosphatemia	II
INSULIN-LIKE GROWTH FACTOR RECEPTOR ANTIBODIES				
IMC-A12	ImClone	IgG1 human anti-IGF-1R monoclonal antibody	• Hyperglycemia	II
PROTEASOME INHIBITORS				
Bortezomib (Velcade, PS-341)	Millennium Pharmaceuticals	Proteasome inhibitor	• Peripheral neuropathy • Nausea/vomiting • Myelosuppression • Fatigue • Rash	II

EGFR, epidermal growth factor receptor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; PDGFR, platelet-derived growth factor receptor; IGF-1R, insulin-like growth factor 1 receptor.

become an alternative or superior choice to cisplatin in the future.

There are certain advantages in the evaluation of novel molecularly targeted agents in previously untreated patients with locally advanced SCCHN. Tumor response can be assessed in this setting (as contrasted with the postoperative setting) and tumor biopsies can be potentially performed to assess treatment effect on a molecular level. Also, there is the potential for achieving a significant clinical benefit that will translate into saving more patient lives, whereas usually smaller or purely palliative benefits can be potentially seen in patients with incurable SCCHN. However, it should be prudent to exclude highly curable patients, for example, with stage III or HPV-positive SCCHN, from studies that evaluate novel CRT regimens until preliminary safety and efficacy is demonstrated in patients with worse prognosis.

Several other questions are generated in the evaluation of novel therapies, especially in the setting of potentially curative therapy: a) is single-agent activity in recurrent or metastatic SCCHN a requirement for the study of a novel agent with IC or CRT in the curative setting; b) how can we best use biomarkers to select patients for targeted therapies; c) which platform chemotherapy or CRT regimens are optimal for the integration of different classes of novel agents; d) is maintenance therapy with a targeted agent required; e) what are the late toxicities of novel combination regimens. The results of the phase I or II trials should be interpreted with caution due to the impact of patient selection and several methodological issues (233). Encouraging clinical results with novel targeted agents derived from phase I and II trials usually require confirmation in randomized clinical trials and should be combined with additional translational research and the identification of predictive biomarkers. Unfortunately, phase III trials tend not to replicate promising results of earlier phase II trials (234).

Finally, simultaneous targeting of 2 or more distinct but partially cross-linked molecular pathways could potentially overcome resistance

and provide an attractive approach for treating SCCHN. Therefore, strategies combining RT and/or chemotherapy with more than 1 targeted agent are of major interest. For example, building on a platform regimen of CRT plus cetuximab by adding an antiangiogenesis agent or an EGFR inhibitor is supported by preclinical data and many clinical investigations of this type are ongoing or planned.

■ KEY POINTS

- Treatment paradigms for locally advanced Squamous Cell Carcinoma of the Head and Neck (SCCHN) have evolved in recent years. Concomitant chemoradiotherapy (CRT) is widely used for the treatment of patients with locally advanced SCCHN, either as primary or as postoperative treatment. However, treatment results remain unsatisfactory.
- The incorporation of novel agents, either cytotoxics or molecularly targeted agents, into induction therapy and/or CRT may improve treatment efficacy and has been the subject of intense clinical investigation.
- The epidermal growth factor receptor (EGFR) inhibitors have an established role in the management of SCCHN. Radiotherapy (RT) and cetuximab, a monoclonal antibody (moAb) against EGFR, improved locoregional control and overall survival (OS) over RT alone and is a treatment option for the treatment of the patients with locally advanced SCCHN. The addition of cetuximab to induction chemotherapy and concurrent CRT regimens has produced very promising results in phase II trials.
- Newer anti-EGFR moAbs, such as nimotuzumab, zalutumumab, and panitumumab, and EGFR tyrosine kinase inhibitors (TKIs), such as erlotinib, gefitinib, and lapatinib, have been evaluated in patients with SCCHN. Currently, their role in combination with CRT is being investigated in phase II and III trials.

- Targeting angiogenesis with agents such as bevacizumab, a monoclonal antibody against the vascular endothelial growth factor (VEGF), is another attractive approach for the treatment of SCCHN. Several studies are evaluating the potential synergistic action of bevacizumab with CRT. VEGF receptor TKIs, such as sorafenib, sunitinib, vandetanib, cediranib, and vatalanib, are also under study.
- Other agents, including antifolates (pemetrexed), agents targeting hypoxic cells (tirapazamine), Src family kinase inhibitors (e.g., dasatinib), insulin-like growth factor receptor antibodies (e.g., IMC-A12), and proteasome inhibitors (e.g., bortezomib) are currently being investigated for the treatment of SCCHN and are in various stages of development.
- The identification of predictive biomarkers that could assist in the selection of patients who benefit the most from a specific molecularly targeted agent may optimize patient outcomes in the future.

■ REFERENCES

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin.* 2005;55(2):74–108.
2. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2008. *CA Cancer J Clin.* 2008;58(2):71–96.
3. Saunders MI, Rojas AM. Management of cancer of the head and neck—a cocktail with your PORT? *N Engl J Med.* 2004;350(19):1997–9.
4. Argiris A, Karamouzis MV, Raben D, Ferris RL. Head and neck cancer. *Lancet.* 2008;371(9625):1695–709.
5. Vineis P, Alavanja M, Buffler P, et al. Tobacco and cancer: recent epidemiological evidence. *J Natl Cancer Inst.* 2004;96(2):99–106.
6. Blot WJ, McLaughlin JK, Winn DM, et al. Smoking and drinking in relation to oral and pharyngeal cancer. *Cancer Res.* 1988;48(11):3282–7.
7. Tuyns AJ, Esteve J, Raymond L, et al. Cancer of the larynx/hypopharynx, tobacco and alcohol: IARC international case-control study in Turin and Varese (Italy), Zaragoza and Navarra (Spain), Geneva (Switzerland) and Calvados (France). *Int J Cancer.* 1988;41(4):483–91.
8. D'Souza G, Kreimer AR, Viscidi R, et al. Case-control study of human papillomavirus and oropharyngeal cancer. *N Engl J Med.* 2007;356(19):1944–56.
9. Gillison ML, Harris J, Westra W, et al. Survival outcomes by tumor human papillomavirus (HPV) status in stage III-IV oropharyngeal cancer (OPC) in RTOG 0129 [ASCO Annual Meeting, abstr 6003]. *J Clin Oncol.* 2009;27:15s.
10. Licitra L, Perrone F, Bossi P, et al. High-risk human papillomavirus affects prognosis in patients with surgically treated oropharyngeal squamous cell carcinoma. *J Clin Oncol.* 2006;24(36):5630–6.
11. Brockstein B, Haraf DJ, Rademaker AW, et al. Patterns of failure, prognostic factors and survival in locoregionally advanced head and neck cancer treated with concomitant chemoradiotherapy: a 9-year, 337-patient, multi-institutional experience. *Ann Oncol.* 2004;15(8):1179–86.
12. Pignon JP, Bourhis J, Domenge C, Designe L. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. *Lancet.* 2000;355(9208):949–55.
13. Bourhis J, Amand C, Pignon J. Update of MACH-NC (Meta-Analysis of Chemotherapy in Head & Neck Cancer) database focused on concomitant chemoradiotherapy [ASCO Annual Meeting, abstr 5505]. *J Clin Oncol.* 2004;22:14S.
14. Pignon JP, le Maitre A, Maillard E, Bourhis J. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. *Radiother Oncol.* 2009;92(1):4–14.
15. Adelstein DJ, Li Y, Adams GL, et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. *J Clin Oncol.* 2003;21(1):92–8.
16. Forastiere AA, Goepfert H, Maor M, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *N Engl J Med.* 2003;349(22):2091–8.
17. Chan AT, Leung SF, Ngan RK, et al. Overall survival after concurrent cisplatin-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma. *J Natl Cancer Inst.* 2005;97(7):536–9.
18. Adelstein DJ, Lavertu P, Saxton JP, et al. Mature results of a phase III randomized trial comparing concurrent chemoradiotherapy with radiation therapy alone in

- patients with stage III and IV squamous cell carcinoma of the head and neck. *Cancer*. 2000;88(4):876–83.
19. Brizel DM, Albers ME, Fisher SR, et al. Hyperfractionated irradiation with or without concurrent chemotherapy for locally advanced head and neck cancer. *N Engl J Med*. 1998;338(25):1798–804.
 20. Wendt TG, Grabenbauer GG, Rodel CM, et al. Simultaneous radiochemotherapy versus radiotherapy alone in advanced head and neck cancer: a randomized multicenter study. *J Clin Oncol*. 1998;16(4):1318–24.
 21. Jeremic B, Shibamoto Y, Stanisavljevic B, Milojevic L, Milicic B, Nikolic N. Radiation therapy alone or with concurrent low-dose daily either cisplatin or carboplatin in locally advanced unresectable squamous cell carcinoma of the head and neck: a prospective randomized trial. *Radiother Oncol*. 1997;43(1):29–37.
 22. Chitapanarux I, Lorvidhaya V, Kamnerdsupaphon P, et al. Chemoradiation comparing cisplatin versus carboplatin in locally advanced nasopharyngeal cancer: randomised, non-inferiority, open trial. *Eur J Cancer*. 2007;43(9):1399–406.
 23. Posner MR, Norris CM, Wirth LJ, et al. Sequential therapy for the locally advanced larynx and hypopharynx cancer subgroup in TAX 324: survival, surgery, and organ preservation. *Ann Oncol*. 2009;20(5):921–7.
 24. Calais G, Alfonsi M, Bardet E, et al. Randomized trial of radiation therapy versus concomitant chemotherapy and radiation therapy for advanced-stage oropharynx carcinoma. *J Natl Cancer Inst*. 1999;91(24):2081–6.
 25. Vokes EE, Stenson K, Rosen FR, et al. Weekly carboplatin and paclitaxel followed by concomitant paclitaxel, fluorouracil, and hydroxyurea chemoradiotherapy: curative and organ-preserving therapy for advanced head and neck cancer. *J Clin Oncol*. 2003;21(2):320–6.
 26. Garden AS, Harris J, Vokes EE, et al. Preliminary results of Radiation Therapy Oncology Group 97-03: a randomized phase ii trial of concurrent radiation and chemotherapy for advanced squamous cell carcinomas of the head and neck. *J Clin Oncol*. 2004;22(14):2856–64.
 27. Weber RS, Berkey BA, Forastiere A, et al. Outcome of salvage total laryngectomy following organ preservation therapy: the Radiation Therapy Oncology Group trial 91-11. *Arch Otolaryngol Head Neck Surg*. 2003;129(1):44–9.
 28. Richey LM, Shores CG, George J, et al. The effectiveness of salvage surgery after the failure of primary concomitant chemoradiation in head and neck cancer. *Otolaryngol Head Neck Surg*. 2007;136(1):98–103.
 29. Bachaud JM, Cohen-Jonathan E, Alzieu C, David JM, Serrano E, Daly-Schveitzer N. Combined postoperative radiotherapy and weekly cisplatin infusion for locally advanced head and neck carcinoma: final report of a randomized trial. *Int J Radiat Oncol Biol Phys*. 1996;36(5):999–1004.
 30. Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *N Engl J Med*. 2004;350(19):1937–44.
 31. Bernier J, Domette C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med*. 2004;350(19):1945–52.
 32. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. The Department of Veterans Affairs Laryngeal Cancer Study Group. *N Engl J Med*. 1991;324(24):1685–90.
 33. Lefebvre JL, Chevalier D, Lubinski B, et al. Is laryngeal preservation (LP) with induction chemotherapy (ICT) safe in the treatment of hypopharyngeal SCC? Final results of the phase III EORTC 24891 trial [ASCO Annual Meeting, abstr 5531]. *J Clin Oncol*. 2004;22:14S(abstr 5531).
 34. Forastiere A, Maor M, Weber R, et al. Long-term results of intergroup RTOG 91-11: a phase III trial to preserve the larynx-induction cisplatin/5-FU and radiation therapy versus concurrent cisplatin and radiation therapy versus radiation therapy [ASCO Annual Meeting, abstr 5517]. *J Clin Oncol*. 2006;24:18S.
 35. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med*. 2006;354(6):567–78.
 36. Argiris A, Jayaram P, Pichardo D. Revisiting induction chemotherapy for head and neck cancer. *Oncology (Williston Park)*. 2005;19(6):759–70.
 37. Schuller DE, Metch B, Stein DW, Mattox D, McCracken JD. Preoperative chemotherapy in advanced resectable head and neck cancer: final report of the Southwest Oncology Group. *Laryngoscope*. 1988;98(11):1205–11.
 38. Domette C, Hill C, Lefebvre JL, et al. Randomized trial of neoadjuvant chemotherapy in oropharyngeal carcinoma. French Groupe d'Etude des Tumeurs de la Tete et du Cou (GETTEC). *Br J Cancer*. 2000;83(12):1594–8.
 39. Paccagnella A, Orlando A, Marchiori C, et al. Phase III trial of initial chemotherapy in stage III or IV head and neck cancers: a study by the Gruppo di Studio

- sui Tumori della Testa e del Collo. *J Natl Cancer Inst.* 1994;86(4):265–72.
40. Adjuvant chemotherapy for advanced head and neck squamous carcinoma. Final report of the Head and Neck Contracts Program. *Cancer.* 1987;60(3):301–11.
 41. Depondt J, Gehanno P, Martin M, et al. Neoadjuvant chemotherapy with carboplatin/5-fluorouracil in head and neck cancer. *Oncology.* 1993;50 Suppl 2:23–7.
 42. Hitt R, Lopez-Pousa A, Martinez-Trufero J, et al. Phase III study comparing cisplatin plus fluorouracil to paclitaxel, cisplatin, and fluorouracil induction chemotherapy followed by chemoradiotherapy in locally advanced head and neck cancer. *J Clin Oncol.* 2005;23(34):8636–45.
 43. Posner MR, Herschock DM, Blajman CR, et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. *N Engl J Med.* 2007;357(17):1705–15.
 44. Vermorken JB, Remenar E, van Herpen C, et al. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. *N Engl J Med.* 2007;357(17):1695–704.
 45. Pointreau Y, Garaud P, Chapet S, et al. Randomized trial of induction chemotherapy with cisplatin and 5-fluorouracil with or without docetaxel for larynx preservation. *J Natl Cancer Inst.* 2009;101(7):498–506.
 46. Hitt R, Grau JJ, Lopez-Pousa A, et al. Final results of a randomized phase III trial comparing induction chemotherapy with cisplatin/5-FU or docetaxel/cisplatin/5-FU follow by chemoradiotherapy (CRT) versus CRT alone as first-line treatment of unresectable locally advanced head and neck cancer (LAHNC) [ASCO Annual Meeting, abstr 6009]. *J Clin Oncol.* 2009;27:15s.
 47. Shih C, Chen VJ, Gossett LS, et al. LY231514, a pyrrolo[2,3-d]pyrimidine-based antifolate that inhibits multiple folate-requiring enzymes. *Cancer Res.* 1997;57(6):1116–23.
 48. Hanna N, Shepherd FA, Fossella FV, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. *J Clin Oncol.* 2004;22(9):1589–97.
 49. Vogelzang NJ, Rusthoven JJ, Symanowski J, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. *J Clin Oncol.* 2003;21(14):2636–44.
 50. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol.* 2008;26(21):3543–51.
 51. Bischof M, Weber KJ, Blatter J, Wannenmacher M, Latz D. Interaction of pemetrexed disodium (ALIMTA, multitargeted antifolate) and irradiation in vitro. *Int J Radiat Oncol Biol Phys.* 2002;52(5):1381–8.
 52. Mauceri HJ, Seetharam S, Salloum RM, Vokes EE, Weichselbaum RR. Treatment of head and neck and esophageal xenografts employing Alimta and concurrent ionizing radiation. *Int J Oncol.* 2001;19(4):833–5.
 53. Bischof M, Huber P, Stoffregen C, Wannenmacher M, Weber KJ. Radiosensitization by pemetrexed of human colon carcinoma cells in different cell cycle phases. *Int J Radiat Oncol Biol Phys.* 2003;57(1):289–92.
 54. Seiwert TY, Connell PP, Mauer AM, et al. A phase I study of pemetrexed, carboplatin, and concurrent radiotherapy in patients with locally advanced or metastatic non-small cell lung or esophageal cancer. *Clin Cancer Res.* 2007;13(2 Pt 1):515–22.
 55. Pivot X, Raymond E, Laguerre B, et al. Pemetrexed disodium in recurrent locally advanced or metastatic squamous cell carcinoma of the head and neck. *Br J Cancer.* 2001;85(5):649–55.
 56. Gibson MK, Smith RP, Heron DE, et al. Phase I trial of pemetrexed, cetuximab, and concurrent radiotherapy (RT) in head and neck cancer (HNC) [ASCO Annual Meeting, abstr 2540]. *J Clin Oncol.* 2008;26(abstr 2540).
 57. Karamouzis MV, Friedland D, Johnson R, Rajasenan K, Branstetter B, Argiris A. Phase II trial of pemetrexed (P) and bevacizumab (B) in patients (pts) with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC): An interim analysis [ASCO Annual Meeting, abstr 6049]. *J Clin Oncol.* 2007;25:18S.
 58. Rischin D, Peters L, Hicks R, et al. Phase I trial of concurrent tirapazamine, cisplatin, and radiotherapy in patients with advanced head and neck cancer. *J Clin Oncol.* 2001;19(2):535–42.
 59. Cohen EE, Rosine D, Haraf DJ, et al. Phase I trial of tirapazamine, cisplatin, and concurrent accelerated boost reirradiation in patients with recurrent head and neck cancer. *Int J Radiat Oncol Biol Phys.* 2007;67(3):678–84.
 60. Rischin D, Peters L, Fisher R, et al. Tirapazamine, Cisplatin, and Radiation versus Fluorouracil, Cisplatin, and Radiation in patients with locally advanced head and neck cancer: a randomized phase II trial of the Trans-Tasman Radiation Oncology Group (TROG 98.02). *J Clin Oncol.* 2005;23(1):79–87.
 61. Rischin D, Peters L, O'Sullivan B, et al. Phase III study of tirapazamine, cisplatin and radiation versus

- cisplatin and radiation for advanced squamous cell carcinoma of the head and neck [ASCO Annual Meeting, abstr LBA6008]. *J Clin Oncol.* 2008;26.
62. Baselga J, Arteaga CL. Critical update and emerging trends in epidermal growth factor receptor targeting in cancer. *J Clin Oncol.* 2005;23(11):2445–59.
 63. Egloff AM, Grandis JR. Targeting epidermal growth factor receptor and SRC pathways in head and neck cancer. *Semin Oncol.* 2008;35(3):286–97.
 64. Grandis J, Melhem M, Gooding W, et al. Levels of TGF- α and EGFR protein in head and neck squamous cell carcinoma and patient survival. *J Natl Cancer Inst.* 1998;90(11):824–32.
 65. Ang KK, Berkey BA, Tu X, et al. Impact of epidermal growth factor receptor expression on survival and pattern of relapse in patients with advanced head and neck carcinoma. *Cancer Res.* 2002;62(24):7350–6.
 66. Karamouzis MV, Grandis JR, Argiris A. Therapies directed against epidermal growth factor receptor in aerodigestive carcinomas. *Jama.* 2007;298(1):70–82.
 67. Ciardiello F. Epidermal growth factor receptor inhibitors in cancer treatment. *Future Oncol.* 2005;1(2):221–34.
 68. Iwase M, Takaoka S, Uchida M, et al. Epidermal growth factor receptor inhibitors enhance susceptibility to Fas-mediated apoptosis in oral squamous cell carcinoma cells. *Oral Oncol.* 2008;44(4):361–8.
 69. Bozec A, Formento P, Ciccolini J, et al. Response of endothelial cells to a dual tyrosine kinase receptor inhibition combined with irradiation. *Mol Cancer Ther.* 2005;4(12):1962–71.
 70. Hirata A, Ogawa S, Kometani T, et al. ZD1839 (Iressa) induces antiangiogenic effects through inhibition of epidermal growth factor receptor tyrosine kinase. *Cancer Res.* 2002;62(9):2554–60.
 71. Bozec A, Peyrade F, Fischel JL, Milano G. Emerging molecular targeted therapies in the treatment of head and neck cancer. *Expert Opin Emerg Drugs.* 2009;14(2):299–310.
 72. Baselga J, Pfister D, Cooper MR, et al. Phase I studies of anti-epidermal growth factor receptor chimeric antibody C225 alone and in combination with cisplatin. *J Clin Oncol.* 2000;18(4):904–14.
 73. Mendelsohn J, Baselga J. Status of epidermal growth factor receptor antagonists in the biology and treatment of cancer. *J Clin Oncol.* 2003;21(14):2787–99.
 74. Huang SM, Harari PM. Modulation of radiation response after epidermal growth factor receptor blockade in squamous cell carcinomas: inhibition of damage repair, cell cycle kinetics, and tumor angiogenesis. *Clin Cancer Res.* 2000;6(6):2166–74.
 75. Milas L, Fan Z, Andratschke NH, Ang KK. Epidermal growth factor receptor and tumor response to radiation: in vivo preclinical studies. *Int J Radiat Oncol Biol Phys.* 2004;58(3):966–71.
 76. Baselga J, Norton L, Masui H, et al. Antitumor effects of doxorubicin in combination with anti-epidermal growth factor receptor monoclonal antibodies. *J Natl Cancer Inst.* 1993;85(16):1327–33.
 77. Fan Z, Baselga J, Masui H, Mendelsohn J. Antitumor effect of anti-epidermal growth factor receptor monoclonal antibodies plus cis-diamminedichloroplatinum on well established A431 cell xenografts. *Cancer Res.* 1993;53(19):4637–42.
 78. Bonner J. Prolongation of survival with the addition of cetuximab to radiation in patients with locoregionally advanced head and neck cancer (SCCHN): five-year results from a randomized trial. American Society for Therapeutic Radiology and Oncology's 50th Annual Meeting, Boston, 2008.
 79. Curran D, Giralt J, Harari PM, et al. Quality of life in head and neck cancer patients after treatment with high-dose radiotherapy alone or in combination with cetuximab. *J Clin Oncol.* 2007;25(16):2191–7.
 80. Pfister DG, Su YB, Kraus DH, et al. Concurrent cetuximab, cisplatin, and concomitant boost radiotherapy for locoregionally advanced, squamous cell head and neck cancer: a pilot phase II study of a new combined-modality paradigm. *J Clin Oncol.* 2006;24(7):1072–8.
 81. Merlano M, Numico G, Russi E, et al. Cetuximab (C-mab) and chemo-radiation (CT-RT) for locoregional advanced squamous cell carcinoma of the head and neck (HNC): A phase II study. [ASCO Annual Meeting, abstr 6043]. *J Clin Oncol.* 2007;25:18S.
 82. Langer CJ, Lee JW, Patel UA, et al. Preliminary analysis of ECOG 3303: Concurrent radiation (RT), cisplatin (DDP) and cetuximab (C) in unresectable, locally advanced (LA) squamous cell carcinoma of the head and neck (SCCHN) [ASCO Annual Meeting, abstr 6006]. *J Clin Oncol.* 2008;26.
 83. Kies M, Harris J, Rotman MZ, et al. Phase II Randomized Trial of Postoperative Chemoradiation Plus Cetuximab for High-Risk Squamous Cell Carcinoma of the Head and Neck (RTOG 0234). ASTRO meeting; 2009;(abstr 1403).
 84. Ma BB, Leung SF, Kam MK, et al. A phase II study of concurrent cetuximab-cisplatin and intensity-modulated radiotherapy (IMRT) in locoregionally advanced nasopharyngeal carcinoma (NPC) with correlation using dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) [ASCO Annual Meeting, abstr 6055]. *J Clin Oncol.* 2008.

85. Argiris AE, Gibson MK, Heron DE, et al. Phase II trial of neoadjuvant docetaxel (T), cisplatin (P), and cetuximab (E) followed by concurrent radiation (X), P, and E in locally advanced head and neck cancer (HNC) [ASCO Annual Meeting, abstr 6002]. *J Clin Oncol.* 2008;26.
86. Lefebvre J, Pointreau Y, Rolland F, et al. Sequential chemoradiotherapy (SCRT) for larynx preservation (LP): Preliminary results of the randomized phase II TREMPIN study [ASCO Annual Meeting, abstr 6010]. *J Clin Oncol.* 2009;27:15s.
87. Kao J, Policarpio L, Teng M, Burri R, Genden E, Packer S. Phase II trial of concurrent 5-fluorouracil, hydroxyurea, cetuximab, and intensity modulated radiation therapy (IMRT) for locally advanced head and neck cancer [ASCO Annual Meeting, abstr 6014]. *J Clin Oncol.* 2009;27:15s.
88. Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med.* 2008;359(11):1116–27.
89. Kies MS, Garden AS, Holsinger C, et al. Induction chemotherapy (CT) with weekly paclitaxel, carboplatin, and cetuximab for squamous cell carcinoma of the head and neck (HN) [ASCO Annual Meeting, abstr 5520]. *J Clin Oncol.* 2006;24:18S.
90. Wanebo HJ, Ghebremichael M, Burtneess B, et al. Phase II evaluation of cetuximab (C225) combined with induction paclitaxel and carboplatin followed by C225, paclitaxel, carboplatin, and radiation for stage III/IV operable squamous cancer of the head and neck (ECOG, E2303) [ASCO Annual Meeting, abstr 6015]. *J Clin Oncol.* 2007;25:18S.
91. Haddad RI, Tishler RB, Norris C, et al. Phase I study of C-TPF in patients with locally advanced squamous cell carcinoma of the head and neck. *J Clin Oncol.* 2009;27(27):4448–53.
92. Mesia R, Vázquez S, Grau JJ, et al. A single-arm phase II trial to evaluate the combination of cetuximab plus docetaxel, cisplatin, and 5-fluorouracil (TPF) as induction chemotherapy (IC) in patients (pts) with unresectable SCCN [ASCO Annual Meeting, abstr 6015]. *J Clin Oncol.* 2009;27:15s.
93. Lopez-Albaitero A, Ferris RL. Immune activation by epidermal growth factor receptor specific monoclonal antibody therapy for head and neck cancer. *Arch Otolaryngol Head Neck Surg.* 2007;133(12):1277–81.
94. Kruser TJ, Armstrong EA, Ghia AJ, et al. Augmentation of radiation response by panitumumab in models of upper aerodigestive tract cancer. *Int J Radiat Oncol Biol Phys.* 2008;72(2):534–42.
95. Wirth LJ, Posner MR, Tishler RB, et al. Phase I study of panitumumab+ chemoradiotherapy (CRT) for head and neck cancer (HNC). [ASCO Annual Meeting, abstr 6007]. *J Clin Oncol.* 2008;26.
96. Ruuls SR, Lammerts van Bueren JJ, van de Winkel JG, Parren PW. Novel human antibody therapeutics: the age of the Umabs. *Biotechnol J.* 2008;3(9–10):1157–71.
97. Bastholt L, Specht L, Jensen K, et al. A novel fully human monoclonal antibody against epidermal growth factor receptor (EGFR). First clinical and FDG-PET imaging results from a Phase I/II trial conducted by the Danish Head and Neck Cancer Study Group (DAHANCA) in patients with squamous cell carcinoma of head and neck (SCCHN) [ASCO Annual Meeting, abstr 5530]. *J Clin Oncol.* 2005; 23:16S.
98. Boku N, Yamazaki K, Yamamoto N, et al. Phase I study of nimotuzumab, a humanized anti-epidermal growth factor receptor (EGFR) IgG1 monoclonal antibody in patients with solid tumors in Japan [ASCO Annual Meeting, abstr e14574]. *J Clin Oncol.* 2009;27.
99. Crombet T, Osorio M, Cruz T, et al. Use of the humanized anti-epidermal growth factor receptor monoclonal antibody h-R3 in combination with radiotherapy in the treatment of locally advanced head and neck cancer patients. *J Clin Oncol.* 2004;22(9):1646–54.
100. Krishnamurthyreddy B, Vidyasagar MS, Koteswar R, et al. A phase IIb 4-arm open-label randomized study to assess the safety and efficacy of h-R3 monoclonal antibody against EGFR in combination with chemoradiation therapy or radiation therapy in patients with advanced (stage III or IVA) inoperable head and neck cancer [ASCO Annual Meeting, abstr 6041]. *J Clin Oncol.* 2009;27:15s.
101. Mendelsohn J, Baselga J. Epidermal growth factor receptor targeting in cancer. *Semin Oncol.* 2006;33(4):369–85.
102. Soulieres D, Senzer NN, Vokes EE, Hidalgo M, Agarwala SS, Siu LL. Multicenter phase II study of erlotinib, an oral epidermal growth factor receptor tyrosine kinase inhibitor, in patients with recurrent or metastatic squamous cell cancer of the head and neck. *J Clin Oncol.* 2004;22(1):77–85.
103. Siu LL, Soulieres D, Chen EX, et al. Phase I/II trial of erlotinib and cisplatin in patients with recurrent or metastatic squamous cell carcinoma of the head and neck: a Princess Margaret Hospital phase II consortium and National Cancer Institute of Canada

- Clinical Trials Group Study. *J Clin Oncol.* 2007; 25(16):2178–83.
104. Kim ES, Kies MS, Glisson BS, et al. Final results of a phase II study of erlotinib, docetaxel and cisplatin in patients with recurrent/metastatic head and neck cancer [ASCO Annual Meeting, abstr 6013]. *J Clin Oncol.* 2007;25:18S.
 105. Savvides P, Agarwala SS, Greskovich J, et al. Phase I study of the EGFR tyrosine kinase inhibitor erlotinib in combination with docetaxel and radiation in locally advanced squamous cell cancer of the head and neck (SCCHN) [ASCO Annual Meeting, abstr 5545]. *J Clin Oncol.* 2006;24:18S (abstr 5545).
 106. Herchenhorn D, Dias FL, Pineda RM, et al. Phase II study of erlotinib combined with cisplatin and radiotherapy for locally advanced squamous cell carcinoma of the head and neck (SCCHN) [ASCO Annual Meeting, abstr 6033]. *J Clin Oncol.* 2007;25:18S.
 107. Arias de la Vega F, Herruzo I, de las Heras M, et al. Erlotinib and chemoradiation in patients with surgically resected locally advanced squamous head and neck cancer (HNSCC): A GICOR phase I study [ASCO Annual Meeting, abstr 6068]. *J Clin Oncol.* 2008;26.
 108. Meluch AA, Spigel D, Burris HA, et al. Combined modality therapy with radiation therapy (RT), chemotherapy, bevacizumab, and erlotinib in the treatment of patients (pts) with locally advanced squamous carcinoma of the head and neck [ASCO Annual Meeting, abstr 6012]. *J Clin Oncol.* 2009;27:15s.
 109. Cohen EE, Rosen F, Stadler WM, et al. Phase II trial of ZD1839 in recurrent or metastatic squamous cell carcinoma of the head and neck. *J Clin Oncol.* 2003;21(10):1980–7.
 110. Cohen EE, Kane MA, List MA, et al. Phase II trial of gefitinib 250 mg daily in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck. *Clin Cancer Res.* 2005;11(23):8418–24.
 111. Kirby AM, A'Hern RP, D'Ambrosio C, et al. Gefitinib (ZD1839, Iressa) as palliative treatment in recurrent or metastatic head and neck cancer. *Br J Cancer.* 2006;94(5):631–6.
 112. Stewart JS, Cohen EE, Licitra L, et al. Phase III study of gefitinib compared with intravenous methotrexate for recurrent squamous cell carcinoma of the head and neck [corrected]. *J Clin Oncol.* 2009;27(11):1864–71.
 113. Argiris A, Ghebremichael M, Gilbert J, Burtness B, Forastiere A. A phase III randomized, placebo-controlled trial of docetaxel (D) with or without gefitinib (G) in recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN): A trial of the Eastern Cooperative Oncology Group (ECOG) [ASCO Annual Meeting, abstr 6011]. *J Clin Oncol.* 2009;27:15s.
 114. Chen C, Kane M, Song J, et al. Phase I trial of gefitinib in combination with radiation or chemoradiation for patients with locally advanced squamous cell head and neck cancer. *J Clin Oncol.* 2007;25(31):4880–6.
 115. Ahmed SM, Cohen EE, Haraf DJ, et al. Updated results of a phase II trial integrating gefitinib (G) into concurrent chemoradiation (CRT) followed by G adjuvant therapy for locally advanced head and neck cancer (HNC) [ASCO Annual Meeting Proceedings, abstr 6028]. *J Clin Oncol.* 2007;25 (pt 1):18S.
 116. Morris JC, Allen C, Citrin D, et al. Pilot phase I study of gefitinib (GEF) in combination with paclitaxel (PAC) and radiation therapy (RT) in patients with locally advanced head and neck squamous cell carcinoma (HNSCC) and effects on epidermal growth factor receptor (EGFR) signaling pathway [ASCO Annual Meeting, abstr 16526]. *J Clin Oncol.* 2007;25:18S.
 117. Rodriguez CP, Adelstein DJ, Saxton JP, et al. Multiagent concurrent chemoradiotherapy (MACCRT) and gefitinib in locoregionally advanced head and neck squamous cell cancer (HNSCC) [ASCO Annual Meeting, abstr 6037]. *J Clin Oncol.* 2009;27:15s.
 118. Hainsworth JD, Spigel DR, Burris HA, 3rd, et al. Neoadjuvant chemotherapy/gefitinib followed by concurrent chemotherapy/radiation therapy/gefitinib for patients with locally advanced squamous carcinoma of the head and neck. *Cancer.* 2009; 115(10):2138–46.
 119. Abidoye OO, Cohen EE, Wong SJ, et al. A phase II study of lapatinib (GW572016) in recurrent/metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN) [ASCO Annual Meeting Part I, abstr 5568]. *J Clin Oncol.* 2006;24:18S.
 120. Montemurro F, Valabrega G, Aglietta M. Lapatinib: a dual inhibitor of EGFR and HER2 tyrosine kinase activity. *Expert Opin Biol Ther.* 2007;7(2):257–68.
 121. Harrington KJ, El-Hariry IA, Holford CS, et al. Phase I study of lapatinib in combination with chemoradiation in patients with locally advanced squamous cell carcinoma of the head and neck. *J Clin Oncol.* 2009;27(7):1100–7.
 122. Specenier PM, Lalami Y, Vermorken J, et al. EORTC 24051: Unexpected side effects of a phase I study

- of TPF induction chemotherapy (IC) followed by chemoradiation (CRT) with lapatinib (LAP), a dual EGFR/Erbb2 inhibitor, in patients with locally advanced larynx and hypopharynx squamous cell carcinoma (LA-LxHxSCC) [ASCO Annual Meeting, abstr 6017]. *J Clin Oncol.* 2009;27:15s.
123. Ongkeko WM, Altuna X, Weisman RA, Wang-Rodriguez J. Expression of protein tyrosine kinases in head and neck squamous cell carcinomas. *Am J Clin Pathol.* 2005;124(1):71–6.
 124. Baselga J, Trigo JM, Bourhis J, et al. Phase II multicenter study of the antiepidermal growth factor receptor monoclonal antibody cetuximab in combination with platinum-based chemotherapy in patients with platinum-refractory metastatic and/or recurrent squamous cell carcinoma of the head and neck. *J Clin Oncol.* 2005;23(24):5568–77.
 125. Kies MS, Ghebremichael MS, Katz TL, Herbst RS, Youssoufian H, Burtneess B. EGFR expression by immunohistochemistry (IHC) and response to chemotherapy and cetuximab in squamous cell carcinoma of the head and neck (SCCHN) [ASCO Annual Meeting, abstr 6024]. *J Clin Oncol.* 2007;25:18S.
 126. Burtneess B, Goldwasser MA, Flood W, Mattar B, Forastiere AA. Phase III randomized trial of cisplatin plus placebo compared with cisplatin plus cetuximab in metastatic/recurrent head and neck cancer: an Eastern Cooperative Oncology Group study. *J Clin Oncol.* 2005;23(34):8646–54.
 127. Chung CH, Ely K, McGavran L, et al. Increased epidermal growth factor receptor gene copy number is associated with poor prognosis in head and neck squamous cell carcinomas. *J Clin Oncol.* 2006;24(25):4170–6.
 128. Temam S, Kawaguchi H, El-Naggar AK, et al. Epidermal growth factor receptor copy number alterations correlate with poor clinical outcome in patients with head and neck squamous cancer. *J Clin Oncol.* 2007;25(16):2164–70.
 129. Freier K, Joos S, Flechtenmacher C, et al. Tissue microarray analysis reveals site-specific prevalence of oncogene amplifications in head and neck squamous cell carcinoma. *Cancer Res.* 2003;63(6):1179–82.
 130. Licitra L, Rolland F, Bokemeyer C, et al. Biomarker potential of EGFR gene copy number by FISH in the phase III EXTREME study: Platinum-based CT plus cetuximab in first-line R/M SCCHN [ASCO Annual Meeting, abstr 6005]. *J Clin Oncol.* 2009;27:15s.
 131. Albanell J, Codony-Servat J, Rojo F, et al. Activated extracellular signal-regulated kinases: association with epidermal growth factor receptor/transforming growth factor alpha expression in head and neck squamous carcinoma and inhibition by anti-epidermal growth factor receptor treatments. *Cancer Res.* 2001;61(17):6500–10.
 132. Grandis JR, Drenning SD, Zeng Q, et al. Constitutive activation of Stat3 signaling abrogates apoptosis in squamous cell carcinogenesis in vivo. *Proc Natl Acad Sci U S A.* 2000;97(8):4227–32.
 133. Xi S, Zhang Q, Gooding WE, Smithgall TE, Grandis JR. Constitutive activation of Stat5b contributes to carcinogenesis in vivo. *Cancer Res.* 2003;63(20):6763–71.
 134. Ferris RL, Feinstein T, Grandis J, et al. Serum biomarkers as predictors of clinical outcome after cetuximab-based therapy in patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN) [ASCO Annual Meeting, abstr 6035]. *J Clin Oncol.* 2009;27:15s.
 135. Loeffler-Ragg J, Witsch-Baumgartner M, Tzankov A, et al. Low incidence of mutations in EGFR kinase domain in Caucasian patients with head and neck squamous cell carcinoma. *Eur J Cancer.* 2006;42(1):109–11.
 136. Perrone F, Suardi S, Pastore E, et al. Molecular and cytogenetic subgroups of oropharyngeal squamous cell carcinoma. *Clin Cancer Res.* 2006;12(22):6643–51.
 137. Sok JC, Coppelli FM, Thomas SM, et al. Mutant epidermal growth factor receptor (EGFRvIII) contributes to head and neck cancer growth and resistance to EGFR targeting. *Clin Cancer Res.* 2006;12(17):5064–73.
 138. Chung CH, Seeley EH, Grigorieva J, et al. Mass spectrometry profile as a predictor of overall survival benefit after treatment with epidermal growth factor receptor inhibitors in head and neck squamous cell carcinoma [ASCO Annual meeting, abstr 6000]. *J Clin Oncol.* 2009;27:15s.
 139. King LE, Jr., Gates RE, Stoscheck CM, Nanney LB. The EGF/TGF alpha receptor in skin. *J Invest Dermatol.* 1990;94(6 Suppl):164S–70S.
 140. Herbst RS, Arquette M, Shin DM, et al. Phase II multicenter study of the epidermal growth factor receptor antibody cetuximab and cisplatin for recurrent and refractory squamous cell carcinoma of the head and neck. *J Clin Oncol.* 2005;23(24):5578–87.
 141. Moriyama M, Kumagai S, Kawashiri S, Kojima K, Kakihara K, Yamamoto E. Immunohistochemical study of tumour angiogenesis in oral squamous cell carcinoma. *Oral Oncol.* 1997;33(5):369–74.

142. Denhart BC, Guidi AJ, Tognazzi K, Dvorak HF, Brown LF. Vascular permeability factor/vascular endothelial growth factor and its receptors in oral and laryngeal squamous cell carcinoma and dysplasia. *Lab Invest.* 1997;77(6):659–64.
143. Inoue K, Ozeki Y, Suganuma T, Sugiura Y, Tanaka S. Vascular endothelial growth factor expression in primary esophageal squamous cell carcinoma. Association with angiogenesis and tumor progression. *Cancer.* 1997;79(2):206–13.
144. Petruzzelli GJ, Benefield J, Taitz AD, et al. Heparin-binding growth factor(s) derived from head and neck squamous cell carcinomas induce endothelial cell proliferations. *Head Neck.* 1997;19(7):576–82.
145. Kyzas PA, Cunha IW, Ioannidis JP. Prognostic significance of vascular endothelial growth factor immunohistochemical expression in head and neck squamous cell carcinoma: a meta-analysis. *Clin Cancer Res.* 2005;11(4):1434–40.
146. Riedel F, Gotte K, Li M, Hormann K, Grandis JR. Abrogation of VEGF expression in human head and neck squamous cell carcinoma decreases angiogenic activity in vitro and in vivo. *Int J Oncol.* 2003;23(3):577–83.
147. Kim KJ, Li B, Winer J, et al. Inhibition of vascular endothelial growth factor-induced angiogenesis suppresses tumour growth in vivo. *Nature.* 1993;362(6423):841–4.
148. Zangari M, Fink LM, Elice F, Zhan F, Adcock DM, Tricot GJ. Thrombotic events in patients with cancer receiving antiangiogenesis agents. *J Clin Oncol.* 2009;27(29):4865–73.
149. Jain RK. Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. *Science* 2005;307(5706):58–62.
150. Gorski DH, Beckett MA, Jaskowiak NT, et al. Blockage of the vascular endothelial growth factor stress response increases the antitumor effects of ionizing radiation. *Cancer Res.* 1999;59(14):3374–8.
151. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med.* 2004;350(23):2335–42.
152. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med.* 2006;355(24):2542–50.
153. Wachsberger P, Burd R, Dicker AP. Tumor response to ionizing radiation combined with antiangiogenesis or vascular targeting agents: exploring mechanisms of interaction. *Clin Cancer Res.* 2003;9(6):1957–71.
154. Shirai K, O'Brien PE. Molecular targets in squamous cell carcinoma of the head and neck. *Curr Treat Options Oncol.* 2007;8(3):239–51.
155. Olsson AK, Dimberg A, Kreuger J, Claesson-Welsh L. VEGF receptor signalling—in control of vascular function. *Nat Rev Mol Cell Biol.* 2006;7(5):359–71.
156. Tabernero J. The role of VEGF and EGFR inhibition: implications for combining anti-VEGF and anti-EGFR agents. *Mol Cancer Res.* 2007;5(3):203–20.
157. Zhong H, Chiles K, Feldser D, et al. Modulation of hypoxia-inducible factor 1 α expression by the epidermal growth factor/phosphatidylinositol 3-kinase/PTEN/AKT/FRAP pathway in human prostate cancer cells: implications for tumor angiogenesis and therapeutics. *Cancer Res.* 2000;60(6):1541–5.
158. Ciardiello F, Bianco R, Damiano V, et al. Antiangiogenic and antitumor activity of anti-epidermal growth factor receptor C225 monoclonal antibody in combination with vascular endothelial growth factor antisense oligonucleotide in human GEO colon cancer cells. *Clin Cancer Res.* 2000;6(9):3739–47.
159. Huang SM, Li J, Armstrong EA, Harari PM. Modulation of radiation response and tumor-induced angiogenesis after epidermal growth factor receptor inhibition by ZD1839 (Iressa). *Cancer Res.* 2002;62(15):4300–6.
160. Perrotte P, Matsumoto T, Inoue K, et al. Anti-epidermal growth factor receptor antibody C225 inhibits angiogenesis in human transitional cell carcinoma growing orthotopically in nude mice. *Clin Cancer Res.* 1999;5(2):257–65.
161. Petit AM, Rak J, Hung MC, et al. Neutralizing antibodies against epidermal growth factor and ErbB-2/neu receptor tyrosine kinases down-regulate vascular endothelial growth factor production by tumor cells in vitro and in vivo: angiogenic implications for signal transduction therapy of solid tumors. *Am J Pathol.* 1997;151(6):1523–30.
162. Ciardiello F, Caputo R, Bianco R, et al. Inhibition of growth factor production and angiogenesis in human cancer cells by ZD1839 (Iressa), a selective epidermal growth factor receptor tyrosine kinase inhibitor. *Clin Cancer Res.* 2001;7(5):1459–65.
163. Cohen EE, Davis DW, Karrison TG, et al. Erlotinib and bevacizumab in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck: a phase I/II study. *Lancet Oncol.* 2009;10(3):247–57.
164. Gibson MK, Kies M, Kim S, et al. Cetuximab (C) and bevacizumab (B) in patients with recurrent or metastatic head and neck squamous cell carcinoma:

- An updated report [ASCO Annual Meeting, abstr 6049]. *J Clin Oncol.* 2009;27:15s.
165. Bozec A, Sudaka A, Fischel JL, Brunstein MC, Etienne-Grimaldi MC, Milano G. Combined effects of bevacizumab with erlotinib and irradiation: a pre-clinical study on a head and neck cancer orthotopic model. *Br J Cancer.* 2008;99(1):93–9.
 166. Seiwert TY, Cohen EE. Targeting angiogenesis in head and neck cancer. *Semin Oncol.* 2008;35(3):274–85.
 167. Auerbach R, Arensman R, Kubai L, Folkman J. Tumor-induced angiogenesis: lack of inhibition by irradiation. *Int J Cancer.* 1975;15(2):241–5.
 168. Katori H, Baba Y, Imagawa Y, et al. Reduction of in vivo tumor growth by MMI-166, a selective matrix metalloproteinase inhibitor, through inhibition of tumor angiogenesis in squamous cell carcinoma cell lines of head and neck. *Cancer Lett.* 2002;178(2):151–9.
 169. Zips D, Krause M, Westphal J. Inhibition of VEGFR tyrosine kinase by ZK 222584/ptk 787 (PTK/ZK) combined with fractionated radiotherapy (RT) in human squamous cell carcinoma (hSCC) in nude mice. 14th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics, Frankfurt, Germany, 2002.
 170. Orhan G, Yigitbasi M, Schiff B. Dual inhibition of EGFR and VEGFR in squamous cell carcinoma of the head and neck: the role of the new EGFR/VEGFR inhibitor NVP-AEE788 AACR-NCI-EORTC International Conference Molecular Targets and Cancer Therapeutics Boston, MA, 2003.
 171. Seiwert TY, Haraf DJ, Cohen EE, et al. Phase I study of bevacizumab added to fluorouracil- and hydroxyurea-based concomitant chemoradiotherapy for poor-prognosis head and neck cancer. *J Clin Oncol.* 2008;26(10):1732–41.
 172. Choong NW, Haraf DJ, Cohen EE, et al. Randomized phase II study of concomitant chemoradiotherapy with 5-fluorouracil-hydroxyurea (FHX) compared to FHX and bevacizumab (BFHX) in intermediate stage head and neck cancer (HNC) [ASCO Annual Meeting, abstr 6034]. *J Clin Oncol.* 2007;25:18S.
 173. Savvides P, Greskovich J, Bokar J, et al. Phase II study of bevacizumab in combination with docetaxel and radiation in locally advanced squamous cell cancer of the head and neck (SCCHN) [ASCO Annual Meeting, abstr 6068]. *J Clin Oncol.* 2007;25:18S.
 174. Pfister DG, Lee NY, Sherman E, et al. Phase II study of bevacizumab (B) plus cisplatin (C) plus intensity-modulated radiation therapy (IMRT) for locoregionally advanced head and neck squamous cell cancer (HNSCC): Preliminary results [ASCO Annual Meeting, abstr 6013]. *J Clin Oncol.* 2009;27:15s.
 175. Elser C, Siu LL, Winkquist E, et al. Phase II trial of sorafenib in patients with recurrent or metastatic squamous cell carcinoma of the head and neck or nasopharyngeal carcinoma. *J Clin Oncol.* 2007;25(24):3766–73.
 176. Williamson SK, Moon J, Huang CH, Guaglianone P, Wolf GT, Urba SG. A phase II trial of sorafenib in patients with recurrent and/or metastatic head and neck squamous cell carcinoma (HNSCC): A Southwest Oncology Group (SWOG) trial [ASCO Annual Meeting, abstr 6044]. *J Clin Oncol.* 2007;25:18S.
 177. Bozec A, Sudaka A, Toussan N, Fischel JL, Etienne-Grimaldi MC, Milano G. Combination of sunitinib, cetuximab and irradiation in an orthotopic head and neck cancer model. *Ann Oncol.* 2009.
 178. Machiels JH, Henry S, Zanetta S, et al. Phase II study of sunitinib in patients with recurrent and/or metastatic squamous head and neck carcinoma: The GORTEC 2006-01 study [ASCO Annual Meeting, abstr 6024]. *J Clin Oncol.* 2009;27:15s.
 179. Fountzilias G, Fragkoulidi A, Kalogera-Fountzila A, et al. A phase II study of sunitinib in patients with recurrent and/or metastatic non-nasopharyngeal head and neck cancer. *Cancer Chemother Pharmacol.* 2009.
 180. Choong NW, Kozloff M, Taber D, et al. Phase II study of sunitinib malate in head and neck squamous cell carcinoma. *Invest New Drugs* 2009.
 181. Fury MG, Zahalsky A, Wong R, et al. A Phase II study of SU5416 in patients with advanced or recurrent head and neck cancers. *Invest New Drugs.* 2007;25(2):165–72.
 182. Sano D, Kawakami M, Fujita K, et al. Antitumor effects of ZD6474 on head and neck squamous cell carcinoma. *Oncol Rep.* 2007;17(2):289–95.
 183. Gustafson DL, Frederick B, Merz AL, Raben D. Dose scheduling of the dual VEGFR and EGFR tyrosine kinase inhibitor vandetanib (ZD6474, Zactima) in combination with radiotherapy in EGFR-positive and EGFR-null human head and neck tumor xenografts. *Cancer Chemother Pharmacol.* 2008;61(2):179–88.
 184. Papadimitrakopoulou V, Frank SJ, Blumenschein GR, et al. Phase I evaluation of vandetanib with radiation therapy (RT) ± cisplatin in previously untreated advanced head and neck squamous cell carcinoma (HNSCC) [ASCO Annual Meeting, abstr 6016]. *J Clin Oncol.* 2009;27:15s.

185. Dreys J, Hofmann I, Hugenschmidt H, et al. Effects of PTK787/ZK 222584, a specific inhibitor of vascular endothelial growth factor receptor tyrosine kinases, on primary tumor, metastasis, vessel density, and blood flow in a murine renal cell carcinoma model. *Cancer Res.* 2000;60(17):4819–24.
186. Wood JM, Bold G, Buchdunger E, et al. PTK787/ZK 222584, a novel and potent inhibitor of vascular endothelial growth factor receptor tyrosine kinases, impairs vascular endothelial growth factor-induced responses and tumor growth after oral administration. *Cancer Res.* 2000;60(8):2178–89.
187. Hess-Stumpp H, Haberey M, Thierauch KH. PTK 787/ZK 222584, a tyrosine kinase inhibitor of all known VEGF receptors, represses tumor growth with high efficacy. *Chembiochem.* 2005;6(3):550–7.
188. Dreys J, Zirrgiebel U, Schmidt-Gersbach CI, et al. Soluble markers for the assessment of biological activity with PTK787/ZK 222584 (PTK/ZK), a vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitor in patients with advanced colorectal cancer from two phase I trials. *Ann Oncol.* 2005;16(4):558–65.
189. Yazici YD, Kim S, Jasser SA, et al. Antivascular therapy of oral tongue squamous cell carcinoma with PTK787. *Laryngoscope.* 2005;115(12):2249–55.
190. Los M, Roodhart JM, Voest EE. Target practice: lessons from phase III trials with bevacizumab and vatalanib in the treatment of advanced colorectal cancer. *Oncologist.* 2007;12(4):443–50.
191. Steeghs N, Nortier JW, Gelderblom H. Small molecule tyrosine kinase inhibitors in the treatment of solid tumors: an update of recent developments. *Ann Surg Oncol.* 2007;14(2):942–53.
192. Kim S, Yazici YD, Barber SE, et al. Growth inhibition of orthotopic anaplastic thyroid carcinoma xenografts in nude mice by PTK787/ZK222584 and CPT-11. *Head Neck.* 2006;28(5):389–99.
193. Miyazawa M, Dong Z, Zhang Z, et al. Effect of PTK/ZK on the angiogenic switch in head and neck tumors. *J Dent Res.* 2008;87(12):1166–71.
194. Bozec A, Lassalle S, Gugenheim J, et al. Enhanced tumour antiangiogenic effects when combining gefitinib with the antivascular agent ZD6126. *Br J Cancer.* 2006;95(6):722–8.
195. Seshadri M, Mazurchuk R, Sperryak JA, Bhattacharya A, Rustum YM, Bellnier DA. Activity of the vascular-disrupting agent 5,6-dimethylxanthone-4-acetic acid against human head and neck carcinoma xenografts. *Neoplasia.* 2006;8(7):534–42.
196. Irby RB, Yeatman TJ. Role of Src expression and activation in human cancer. *Oncogene.* 2000;19(49):5636–42.
197. Summy JM, Gallick GE. Src family kinases in tumor progression and metastasis. *Cancer Metastasis Rev.* 2003;22(4):337–58.
198. Lombardo LJ, Lee FY, Chen P, et al. Discovery of N-(2-chloro-6-methyl-phenyl)-2-(6-(4-(2-hydroxyethyl)-piperazin-1-yl)-2-methylpyrimidin-4-ylamino)thiazole-5-carboxamide (BMS-354825), a dual Src/Abl kinase inhibitor with potent antitumor activity in preclinical assays. *J Med Chem.* 2004;47(27):6658–61.
199. Johnson FM, Saigal B, Talpaz M, Donato NJ. Dasatinib (BMS-354825) tyrosine kinase inhibitor suppresses invasion and induces cell cycle arrest and apoptosis of head and neck squamous cell carcinoma and non-small cell lung cancer cells. *Clin Cancer Res.* 2005;11(19 Pt 1):6924–32.
200. Brooks HD, Glisson B, Lu C, et al. Phase II study of dasatinib in the treatment of head and neck squamous cell carcinoma (HNSCC) [ASCO Annual Meeting, abstr 6022]. *J Clin Oncol.* 2009;27:15s.
201. Manley PW, Cowan-Jacob SW, Mestan J. Advances in the structural biology, design and clinical development of Bcr-Abl kinase inhibitors for the treatment of chronic myeloid leukaemia. *Biochim Biophys Acta.* 2005;1754(1–2):3–13.
202. Koppikar P, Choi SH, Egloff AM, et al. Combined inhibition of c-Src and epidermal growth factor receptor abrogates growth and invasion of head and neck squamous cell carcinoma. *Clin Cancer Res.* 2008;14(13):4284–91.
203. Maa MC, Leu TH, McCarley DJ, Schatzman RC, Parsons SJ. Potentiation of epidermal growth factor receptor-mediated oncogenesis by c-Src: implications for the etiology of multiple human cancers. *Proc Natl Acad Sci U S A.* 1995;92(15):6981–5.
204. Kopetz S, Wu J, Davies M, Johnson F, Donato N. Synergistic effects of combination therapy with anti-EGFR and anti-Src therapy in vitro in colon cancer [abstr 406]. *Gastrointestinal Cancer Symposium American Society of Clinical Oncology.* 2007.
205. Feinstein TM, Agrawal S, Stoller RG, Egorin MJ, Argiris A. Phase I and pharmacokinetic (PK) study of dasatinib (D) and cetuximab (C) in patients (pts) with advanced solid malignancies [ASCO Annual Meeting, abstr 3540]. *J Clin Oncol.* 2009;27:15s.
206. Reinmuth N, Fan F, Liu W, et al. Impact of insulin-like growth factor receptor-I function on angiogenesis, growth, and metastasis of colon cancer. *Lab Invest.* 2002;82(10):1377–89.

207. Zeng H, Datta K, Neid M, Li J, Parangi S, Mukhopadhyay D. Requirement of different signaling pathways mediated by insulin-like growth factor-I receptor for proliferation, invasion, and VPF/VEGF expression in a pancreatic carcinoma cell line. *Biochem Biophys Res Commun*. 2003;302(1):46–55.
208. Zhang X, Lin M, van Golen KL, Yoshioka K, Itoh K, Yee D. Multiple signaling pathways are activated during insulin-like growth factor-I (IGF-I) stimulated breast cancer cell migration. *Breast Cancer Res Treat*. 2005;93(2):159–68.
209. Barnes CJ, Ohshiro K, Rayala SK, El-Naggar AK, Kumar R. Insulin-like growth factor receptor as a therapeutic target in head and neck cancer. *Clin Cancer Res*. 2007;13(14):4291–9.
210. Chen Z, Ricker JL, Malhotra PS, et al. Differential bortezomib sensitivity in head and neck cancer lines corresponds to proteasome, nuclear factor-kappaB and activator protein-1 related mechanisms. *Mol Cancer Ther*. 2008;7(7):1949–60.
211. Eferi R, Wagner E. AP-1: a double-edged sword in tumorigenesis. *Nat Rev Cancer*. 2003;3(11):859–68.
212. Van Waes C. Nuclear factor-kB in development, prevention, and therapy of cancer. *Clin Cancer Res*. 2007;13:1076–82.
213. Ondrey FG, Dong G, Sunwoo J, et al. Constitutive activation of transcription factors NF-(kappa)B, AP-1, and NF-IL6 in human head and neck squamous cell carcinoma cell lines that express pro-inflammatory and pro-angiogenic cytokines. *Mol Carcinog*. 1999;26(2):119–29.
214. Duffey DC, Chen Z, Dong G, et al. Expression of a dominant-negative mutant inhibitor-kappaBalpha of nuclear factor-kappaB in human head and neck squamous cell carcinoma inhibits survival, proinflammatory cytokine expression, and tumor growth in vivo. *Cancer Res*. 1999;59(14):3468–74.
215. Loercher A, Lee TL, Ricker JL, et al. Nuclear factor-kappaB is an important modulator of the altered gene expression profile and malignant phenotype in squamous cell carcinoma. *Cancer Res*. 2004;64(18):6511–23.
216. Sunwoo JB, Chen Z, Dong G, et al. Novel proteasome inhibitor PS-341 inhibits activation of nuclear factor-kappa B, cell survival, tumor growth, and angiogenesis in squamous cell carcinoma. *Clin Cancer Res*. 2001;7(5):1419–28.
217. An J, Sun Y, Fisher M, Rettig MB. Maximal apoptosis of renal cell carcinoma by the proteasome inhibitor bortezomib is nuclear factor-kappaB dependent. *Mol Cancer Ther*. 2004;3(6):727–36.
218. Podar K, Raab MS, Tonon G, et al. Up-regulation of c-Jun inhibits proliferation and induces apoptosis via caspase-triggered c-Abl cleavage in human multiple myeloma. *Cancer Res*. 2007;67(4):1680–8.
219. Tai YT, Fulciniti M, Hideshima T, et al. Targeting MEK induces myeloma-cell cytotoxicity and inhibits osteoclastogenesis. *Blood*. 2007;110(5):1656–63.
220. Kojima K, Konopleva M, Samudio IJ, Ruvalo V, Andreeff M. Mitogen-activated protein kinase kinase inhibition enhances nuclear proapoptotic function of p53 in acute myelogenous leukemia cells. *Cancer Res*. 2007;67(7):3210–9.
221. Williams S, Pettaway C, Song R, Papandreou C, Logothetis C, McConkey DJ. Differential effects of the proteasome inhibitor bortezomib on apoptosis and angiogenesis in human prostate tumor xenografts. *Mol Cancer Ther*. 2003;2(9):835–43.
222. Duan J, Friedman J, Nottingham L, Chen Z, Ara G, Van Waes C. Nuclear factor-kappaB p65 small interfering RNA or proteasome inhibitor bortezomib sensitizes head and neck squamous cell carcinomas to classic histone deacetylase inhibitors and novel histone deacetylase inhibitor PXD101. *Mol Cancer Ther*. 2007;6(1):37–50.
223. Nawrocki ST, Bruns CJ, Harbison MT, et al. Effects of the proteasome inhibitor PS-341 on apoptosis and angiogenesis in orthotopic human pancreatic tumor xenografts. *Mol Cancer Ther*. 2002;1(14):1243–53.
224. Kubicek GJ, Machtay M, Axelrod RA, et al. Phase I trial of bortezomib (VELCADE), cisplatin and radiotherapy for advanced head and neck cancer [ASCO Annual Meeting, abstr 6028]. *J Clin Oncol*. 2008;26.
225. Gilbert J, Lee J, Argiris A, et al. Phase II randomized trial of bortezomib (B) plus irinotecan (I) or B with addition of I at progression in recurrent (R) or metastatic (M) squamous cell carcinoma of the head and neck (SCCHN) (E1304): A trial of the Eastern Cooperative Oncology Group [ASCO Annual Meeting, abstr 6020]. *J Clin Oncol*. 2009;27:15s.
226. Siu LL. Promising new targeted agents in head and neck cancer. *Int J Radiat Oncol Biol Phys*. 2007;69 (2 Suppl):S59–60.
227. Amornphimoltham P, Patel V, Sodhi A, et al. Mammalian target of rapamycin, a molecular target in squamous cell carcinomas of the head and neck. *Cancer Res*. 2005;65(21):9953–61.
228. Thiagalingam S, Cheng KH, Lee HJ, Mineva N, Thiagalingam A, Ponte JF. Histone deacetylases: unique players in shaping the epigenetic histone code. *Ann N Y Acad Sci*. 2003;983:84–100.

229. Marks PA, Richon VM, Rifkind RA. Histone deacetylase inhibitors: inducers of differentiation or apoptosis of transformed cells. *J Natl Cancer Inst.* 2000;92(15):1210–6.
230. Monneret C. Histone deacetylase inhibitors for epigenetic therapy of cancer. *Anticancer Drugs.* 2007;18(4):363–70.
231. Richon VM, Sandhoff TW, Rifkind RA, Marks PA. Histone deacetylase inhibitor selectively induces p21WAF1 expression and gene-associated histone acetylation. *Proc Natl Acad Sci U S A.* 2000; 97(18):10014–9.
232. Blumenschein GR, Jr., Kies MS, Papadimitrakopoulou VA, et al. Phase II trial of the histone deacetylase inhibitor vorinostat (Zolinza, suberoylanilide hydroxamic acid, SAHA) in patients with recurrent and/or metastatic head and neck cancer. *Invest New Drugs.* 2008;26(1):81–7.
233. Hamberg P, Verweij J. Phase I drug combination trial design: walking the tightrope. *J Clin Oncol.* 2009; 27(27):4441–3.
234. Zia MI, Siu LL, Pond GR, Chen EX. Comparison of outcomes of phase II studies and subsequent randomized control studies using identical chemotherapeutic regimens. *J Clin Oncol.* 2005;23(28):6982–91.

CHAPTER 7

Concurrent Chemoradiotherapy in Head and Neck Cancer

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■ BACKGROUND

Squamous cell carcinomas of the head and neck represent approximately 5% of newly diagnosed cancers annually worldwide (1). The estimated number of new cases and number of deaths from head and neck cancers in the United States in 2009 are roughly 48 000 and 11 000, respectively (1). Although survival rates have improved over the last few decades, local recurrences and distant metastases remain high, leading to suboptimal outcomes. Furthermore, new cases of oropharyngeal squamous cell carcinomas continue to rise steadily due to the epidemic of human papillomavirus (HPV) as an etiologic factor (2). Despite HPV being a novel risk factor for oropharyngeal squamous cell carcinoma, tobacco and alcohol remain the strongest risk factors for head and neck cancer.

Until recently, surgery was the mainstay of treatment for most head and neck malignancies. Surgery often results in significant morbidity, particularly with regard to speech and swallowing dysfunction. However, during the last 2 decades the management of head and neck cancer has changed dramatically, mostly due to the development of an organ preservation approach using chemoradiotherapy (CRT) as definitive therapy. As a general rule, advanced head and neck tumors are managed

with multimodality therapy, which includes various combinations of surgery, radiotherapy (RT), chemotherapy and, more recently, also biologically targeted agents. Therefore, treatment of advanced head and neck cancer should be managed by a multidisciplinary team including specialists in head and neck surgery, radiation oncology, and medical oncology, as well as experts from other fields such as reconstructive surgery and rehabilitation medicine.

Various CRT regimens have been investigated. Chemotherapy can be administered concurrently with RT, or sequentially, either before (neoadjuvant or induction chemotherapy) or after definitive therapy (adjuvant chemotherapy). A recent update of the Meta-Analysis of Chemotherapy in Head and Neck Cancer demonstrated an absolute survival benefit for CRT over RT alone of 4.5% at 5 years (3). The benefit was significantly greater for concurrent CRT (6.5% at 5 years) as compared to induction chemotherapy (IC) (2.4% at 5 years). No clear advantage was demonstrated for adjuvant chemotherapy. Concurrent CRT had a pronounced effect on locoregional control, which was not observed for IC. On the other hand, IC provided a more pronounced effect on distant metastases compared to concurrent chemotherapy. No

significant difference was seen between monotherapy and polychemotherapy. In the monotherapy group, the effect of platinum agents was significantly higher than that of other monotherapies. The effect of chemotherapy on survival was not altered by sex, performance status, or tumor site. However, the effect of chemotherapy on survival significantly decreased with increasing age and completely disappeared in patients older than 70 years. Possible explanations are the higher proportion of deaths due to other causes than head and neck cancer or an increase in treatment-related mortality in the older age group.

Similarly, advances in RT have evolved, particularly with the use of intensity-modulated radiation therapy (IMRT), a technology that improves our ability to shape the radiation dose and conform it to the target, allowing better normal tissue sparing. Studies comparing IMRT to conventional RT are currently underway. Altered fractionation RT has also been shown to improve locoregional control and overall survival in patients with advanced head and neck cancer (4).

The treatment of head and neck cancer should be individualized according to characteristics of the tumor, including the primary site, tumor and nodal stage, and pathologic features, such as grade, perineural invasion, and lymphovascular invasion. Patient factors such as age, comorbidities, performance status, and personal preferences should also be taken into account. Availability of therapies and local expertise are additional considerations. In general, cancers originating in the oral cavity and paranasal sinuses require surgical ablation, with or without adjuvant CRT, depending on clinical and pathological features (see “Adjuvant Therapy”). On the other hand, advanced nasopharyngeal, oropharyngeal, and hypopharyngeal tumors and the majority of advanced-stage laryngeal cancers are preferentially treated with definitive concurrent CRT in most centers. This chapter focuses on the biological basis for combined modality therapy and on the evidence-based data for its use in the management of locally advanced head and neck cancers.

■ THE RATIONALE FOR CRT IN HEAD AND NECK CANCER

Although there is abundant clinical evidence for the better outcome with combined CRT over RT alone, the biological mechanisms underlying this effect are still not fully understood. In 1979, Steel proposed a theoretical framework to describe the interaction between RT and chemotherapy (5,6). One of the proposed models was spatial cooperation, according to which RT acts locoregionally while chemotherapy acts systemically against distant micrometastases. Spatial cooperation does not require any interaction between the 2 modalities. It also assumes independent and nonoverlapping toxicity profiles of RT and chemotherapy to allow their use at effective doses without increasing normal tissue toxicity. However, the concurrent use of chemotherapy and RT does increase acute toxicity, which, in most cases, precludes the delivery of systemically effective chemotherapy doses and schedules.

Sequential administration of chemotherapy followed by RT could potentially allow the administration of these 2 modalities at their full dose. However, clinically, this approach has generally failed to improve overall survival or disease-free survival as compared with radiation alone or with concurrent CRT.

Concurrent CRT with lower “radiosensitizing” doses of chemotherapy has, in general, failed to decrease the incidence of distant metastases as compared with radiation alone (3,7–11). The few trials of concurrent CRT that demonstrated better distant control compared with radiation alone (12,13) may indicate that radiosensitizing doses of chemotherapy have some systemic spatial cooperative effect or that improved locoregional control, achieved by concurrent CRT, decreases subsequent metastases (14).

The other proposed model assumes interaction between chemotherapy and RT within the radiation field. This interaction may result in enhanced tumor response, which can be to the same degree as (additive) or more than (supra-additive) the summation of the expected effects of

each modality alone. The drug–radiation interaction may also result in infra-additivity, in which case the addition of chemotherapy to radiation inhibits tumor response or protects normal tissue.

The term *radiosensitization* is used to describe the supra-additive tumor response to combined treatment. “True” radiosensitizers are devoid of any cytotoxic activity. However, the most commonly used radiosensitizers have inherent cytotoxic activity and can increase damage to normal tissues. When radiosensitizing chemotherapy is combined with radiation, both tumor and normal tissue dose-response curves produced by radiation alone shift to the left. Ideally, radiation sensitizers should influence the tumor response curve more than the normal tissue curve, meaning that the increase in antitumor effect is larger than the increase in normal tissue damage.

Damage to DNA is considered the principal mechanism by which ionizing radiation injures cells and tissues. Ionizing radiation induces a wide range of DNA lesions, including base damage, alkali-labile sites, single-strand breaks (SSBs) and double-strand breaks (DSBs). Most of these DNA lesions are rapidly repaired, with the exception of DSBs. It is thought that DSBs represent the principal damage that, if not adequately repaired, may directly or indirectly lead to cell death (15). Additional possible mechanisms of radiation cytotoxicity include apoptosis triggered by radiation damage to cell membranes, direct radiation damage to mitochondria, and damage to the microvasculature that supports the tumor (15).

The interaction between radiosensitizers and radiation can occur at the molecular, cellular, and tissue level. At the molecular level, DNA damage induced by both chemotherapy and RT may act synergistically to enhance cell kill. Platinum compounds, which are among the most widely used chemotherapeutic agents in combination with radiation, interact with nucleophilic N7 sites of purine bases and thus introduce DNA intrastrand and interstrand cross-links. Although a cisplatin DNA adduct or a radiation-induced SSB may be rapidly repaired, the presence of both lesions in

close proximity may act synergistically to make the defect significantly more difficult to repair. This type of interaction is supported by mathematical probability models (16) as well as experimental data (17,18). In addition, studies suggest enhanced production of radiation-induced single- and double-strand breaks in the presence of a platinum compound (19) as well as enhanced formation of toxic platinum intermediates in the presence of radiation-induced free radicals (20).

Radiosensitization can result from chemotherapy-induced increase in DNA lethal lesions or from inhibition of their repair. The latter has been implicated in platinum compounds (21–23) and even more so with antimetabolite radiosensitizers (24). All antimetabolite radiosensitizers target DNA replication. Their cytotoxicity is mediated through inhibition of synthesis of deoxyribonucleotides or production of fraudulent substrates for DNA synthesis. Antimetabolites are most active in early S-phase, and elimination of S-phase cells, which are relatively radioresistant, was postulated as their mechanism of radiosensitization. However, this seems unlikely to be the principal mechanism, because significant radiosensitization is observed even in noncytotoxic concentrations of these drugs. 5-Fluorouracil (5-FU) and its oral prodrugs capecitabine and uracil/ftorafur deplete the cellular pools of deoxythymidine triphosphate through inhibition of thymidylate synthase, resulting in inhibition of DNA synthesis and futile repair cycles. 5-fluoro-2'-deoxyuridine has been shown to slow the repair of DNA DSBs, leading to enhanced cell killing with radiation (25). The nucleoside analog gemcitabine is a potent radiosensitizer. Its active metabolite, which is a fraudulent nucleotide, directly inhibits DNA polymerases, and its incorporation into DNA slows replication. However, incorporation into DNA does not seem to affect radiosensitization.

The latter has been shown to correlate with the inhibition of ribonucleotide reductase and the resultant depleted pools of deoxyadenosine triphosphate (dATP) (26). In vitro studies have not demonstrated increased DNA DSBs or inhibition

of their repair with the addition of gemcitabine to radiation. Cells are not redistributed to a more radiosensitive phase of the cell cycle, but rather accumulation of cells in S phase appears to be required for maximal radiosensitization (27), as is the case with 5-FU. It has been postulated that the depletion of dATP results in mismatches in DNA that, if not repaired, augment cell killing with radiation (24). Clinical trials of concurrent CRT, with gemcitabine in head and neck cancer, reported significant toxicity, suggesting that inhibition of repair mechanisms may play a significant role (28).

At the cellular level, the term *cytokinetic cooperation* was coined to describe the increased radiation susceptibility observed with the addition of drugs that are S-phase specific to radiation. The S phase is considered to be the most radioresistant phase in the cell cycle, whereas G2-M phases are considered to be the most radiosensitive phases (15). Since the drug is inactive against non-S-phase cells and is assumed to not affect the radiation response among survivor cells, this interaction is usually additive.

Synchronization of cells to the radiosensitive M phase has been proposed as the mechanism of radiosensitization for paclitaxel and docetaxel (29,30). These drugs bind to microtubules, alter their dynamics, and inhibit the formation of the mitotic spindle, thus blocking the progression of cells through mitosis. However, studies have shown that this cell-cycle pooling, if at all it occurs in vivo, may not be sufficient to explain the increased radiation sensitivity with the addition of these drugs (31).

At the tissue level, chemotherapy-induced tumor shrinkage may improve perfusion, leading to improved oxygenation and increased radiosensitivity due to reduced hypoxic areas, which are relatively radioresistant. This usually requires sequential administration of chemotherapy followed by radiation. Certain chemotherapeutic agents, such as mitomycin C and paclitaxel, are considered to be preferentially active against hypoxic cells.

Chemotherapy may also inhibit the proliferation of tumor cells that takes place in the interval

between radiation fractions ("repopulation"), which is considered to be an important cause of treatment failure (32). Inhibition of repopulation is thought to be the main mechanism of radiosensitization of epidermal growth factor receptor (EGFR) inhibitors (33,34). This type of interaction requires concurrent administration of the 2 modalities.

The mechanisms by which chemotherapy enhances the effect of radiation are likely to be complex and to involve more than one simple interaction. Better understanding of these mechanisms will allow us to optimize the timing and dosing of chemotherapy in relation to radiation and improve clinical outcome.

■ CLINICAL DATA

Surgery Versus Concurrent CRT

Soo et al (35) compared primary surgery followed by adjuvant RT with concurrent CRT in the management of squamous cell cancer of the head and neck. In this trial, 119 patients with newly diagnosed stage III/IV cancers, excluding nasopharyngeal and salivary gland tumors, were randomized to receive either surgical resection with neck dissection followed by RT or definitive concurrent CRT. Specifically, the CRT arm consisted of 2 cycles of cisplatin at 20 mg/m²/day and 5-fluorouracil at 1000 mg/m²/day as a continuous infusion on days 1 and 28 of the concurrent RT course, which consisted of 66 Gy in 33 fractions given in six and a half weeks. Patients in the CRT arm underwent salvage surgery if they had persistent disease at 6 to 8 weeks posttreatment. The median follow-up was 6 years, and after 3 years, there was no statistical difference in disease-free or overall survival between the 2 treatment arms. The organ preservation rate was 45%, with a higher rate among laryngeal/hypopharyngeal tumors (68%) than other tumors (30%). The main criticism of this study is the small sample size. Otherwise, this study highlights the benefits of concurrent CRT as comparable to the survival rates of primary surgery with RT, while providing the benefit of organ preservation.

Concurrent CRT by Site

Oropharynx

Squamous cell carcinoma of the oropharynx, including tumors of the tonsils, base of tongue, soft palate, and pharyngeal wall, has historically been treated with surgical resection regardless of tumor stage. Today, stage I and II lesions are typically treated with primary surgery or RT. The treatment of locally advanced stage III and IV oropharyngeal cancers, usually involves RT and chemotherapy with or without surgical intervention. The preferred treatment for patients with advanced oropharyngeal cancer is concurrent CRT followed by neck dissection as clinically indicated or salvage surgery for treatment failure at the primary site. Other options include up-front surgery followed by adjuvant CRT in patients with high-risk features, as discussed later in this chapter (see “adjuvant concurrent CRT”).

In 2004, the French Head and Neck Oncology and Radiotherapy Group (GORTEC) published the results of their 94-01 trial, which demonstrated that concurrent CRT improved overall survival and locoregional control rates compared to RT alone in patients with oropharyngeal cancer (8). These investigators randomly assigned 226 patients with stage III or IV oropharyngeal cancer to receive RT alone (70 Gy, 2 Gy/fraction, for 7 weeks) or RT (same regimen) with carboplatin (70 mg/m²/day for 4 days) and fluorouracil (continuous infusion of 600 mg/m²/day for 4 days) for 3 cycles starting on days 1, 22, and 43 of RT. With a median follow-up of 5.5 years, overall survival was better in the concurrent CRT arm than that for the RT-alone arm (22.4% vs. 15.8%; $P = .05$). Locoregional control was also better in the concurrent CRT arm than that for the RT-alone arm (47.6% vs. 24.7%; $P = .002$).

Adelstein et al (7) reported the results of an intergroup phase III trial that randomized patients with unresectable head and neck cancer to 1 of 3 arms: RT alone (70 Gy); RT with concurrent high-dose single agent cisplatin (100 mg/m² on days 1, 22, and 43); or split-course RT with

concurrent cisplatin and 5-fluorouracil. The most common primary tumor site was the oropharynx, accounting for nearly 60% of the 271 analyzable patients. With a median follow-up of 41 months, conventional RT with concurrent cisplatin resulted in superior 3-year overall survival (37%) compared to RT alone (23%) or split-course RT with concurrent cisplatin/5-fluorouracil (27%). The rate of distant metastases as the first site of recurrence did not differ among the 3 treatment arms.

Nasopharynx

Nasopharyngeal carcinoma differs from other head and neck cancers in its epidemiology, pathology, and response to treatment. Given its close proximity to the skull base and neurovascular structures, surgery is generally not a treatment option for patients with nasopharyngeal cancer. RT has been the mainstay of treatment for cancers of the nasopharynx for many years. However, for advanced-stage nasopharyngeal cancer, concurrent CRT has now become the standard of care.

The US Intergroup Trial 00-99 was the first randomized study to show significant survival benefit to concurrent CRT followed by adjuvant chemotherapy in locally advanced nasopharyngeal cancer (12). This study randomized 147 patients with stage III and IV nasopharyngeal cancer to receive either RT alone (70 Gy in 35 fractions over 7 weeks) or the same RT with concurrent cisplatin (100 mg/m² on days 1, 22, and 43) followed by 3 courses of cisplatin and 5-FU given every 4 weeks after the completion of CRT. In the initial report, the concurrent and adjuvant chemotherapy arm had an impressive 30% improvement in 3-year overall survival rate over RT alone (76% vs. 46%; $P < .001$). In an update, presented in 2001 at the Annual Meeting of the American Society of Clinical Oncology, this advantage was maintained (36). Five-year overall survival was 67% versus 37%, and disease-free survival was 74% versus 46% in favor of the concurrent and adjuvant chemotherapy (both P values $< .001$).

Following the intergroup trial, other studies of CRT in locally advanced nasopharyngeal cancer have been conducted. Some of the larger randomized trials are summarized in Table 7.1 (13,37–39). A meta-analysis of 8 trials including 1753 patients with locally advanced nasopharyngeal cancer demonstrated an absolute survival benefit of 6% at 5 years for CRT compared to RT alone. This benefit was essentially observed when chemotherapy was administered concurrently with RT (40). The roles of induction and adjuvant chemotherapy given alone or added to concurrent CRT were questionable. Another meta-analysis of 10 randomized studies including 2450 patients with locally advanced nasopharyngeal cancer found an absolute survival benefit of 20% after 3 years in the concurrent CRT group. No significant benefit on overall survival was found for neoadjuvant and/or adjuvant chemotherapy (41). Concurrent CRT was found to improve both locoregional control and the rate of distant failures.

Induction chemotherapy followed by concurrent CRT is another treatment option that is being investigated. In a randomized phase II study, IC with cisplatin and docetaxel followed by concurrent CRT was compared with concurrent CRT alone. The neoadjuvant regimen was well tolerated and allowed subsequent delivery of full-dose CRT. Preliminary results suggested a positive impact on survival (42).

Larynx

Laryngeal cancers are often discovered at an earlier stage than most head and neck cancers because they tend to cause hoarseness, a noticeable symptom. Stage I and II laryngeal cancer is currently treated with either surgical resection or definitive RT. For locally advanced laryngeal carcinoma (stage III or IV), total laryngectomy with or without postoperative RT used to be the standard of care. However, over the past 2 decades, organ preservation approaches using CRT have been established as an alternative to total laryngectomy, sparing the patients the substantial functional morbidity

associated with this surgery. Total laryngectomy is currently reserved for tumor with extensive cartilage invasion and for tumors with extralaryngeal involvement, or it is used as salvage therapy.

Attempts to preserve the larynx in advanced disease with the use of RT alone resulted in inferior survival rates compared to upfront total laryngectomy (43). In the landmark trial of the Department of Veterans Affairs Laryngeal Cancer Group, published in 1991, 332 patients with stage III–IV laryngeal cancer were randomized to 1 of 2 arms: IC (cisplatin and 5-fluorouracil) followed by conventional RT or upfront laryngectomy plus adjuvant RT (44). The larynx was preserved in 64% of the patients assigned to IC without compromising the overall survival compared to the upfront surgery group. This study established the role of IC followed by RT as an alternative to total laryngectomy for patients with locally advanced laryngeal cancer. However, patients with T4 primary tumors had a higher rate of salvage laryngectomy (56%) than that of those with smaller primary tumors (29%).

The Radiation Therapy Oncology Group and the Head and Neck Intergroup conducted a randomized trial (RTOG 91-11) to investigate 3 radiation-based strategies for larynx preservation: RT alone, IC followed by RT, or concurrent CRT (45). RT consisted of 70 Gy to the primary tumor and clinically positive nodes, given in 35 fractions over a 7-week period in all treatment arms. The entire neck was also irradiated with a minimum of 50 Gy. Patients assigned to the IC arm, which underwent salvage surgery because of a poor response to chemotherapy, received adjuvant RT of 50 to 70 Gy, depending on their surgical margin status. Induction chemotherapy consisted of cisplatin 100 mg/m² on day 1 and continuous 5-FU 1000 mg/m²/day for days 1 to 5 given every 3 weeks for 2 courses (a regimen identical to that given in the Department of Veterans Affairs Laryngeal Cancer Group study). Patients with complete or partial response went on to receive a third course of cisplatin and 5-FU. Those with less than a partial response

TABLE 7.1
Randomized Trials of Chemoradiotherapy versus Radiotherapy in Locally Advanced Nasopharynx Cancer

	N	Stage	WHO Type	Median Follow-up	Treatment Arms	Time Point	LRC	DMfs (%)	PFS (%)	OS (%)
Wee et al (13)	221	T3-4NxM0 TxN2-3M0 (UICC 1997)	II-III	3.2 years	RT alone (70 Gy) Concurrent CRT (DDP 25 mg/m ² /day for 4 days on weeks 1, 4, and 7 of RT Adjuvant DDP/5FU	2 years		70 87*		78 85*
Chan et al (37)	350	II-IV (UICC 1997)	II-III (1% type I)	5.5 years	RT alone (66 Gy, optional parapharyngeal boost of 10-20 Gy) Concurrent CRT with weekly DDP (40 mg/m ²)	5 years			52.1 60.2**	58.6 70.3**
Lin et al (38)	284	III-IV (UICC 1992)	II-III (3% type I)	5.4 years	RT alone (70-74 Gy) Concurrent CRT (DDP 20 mg/m ² /day and 5FU 400 mg/m ² /day as a 96-hour infusion during weeks 1 and 5 of RT)	5 years		69.9 78.7	53 71.6*	54.2 72.3*
Chen et al (39)	316	T3-4NxM0 TxN2-3M0 (UICC 1997)	II-III	2.4 years	RT alone (70 Gy) Concurrent CRT with weekly DDP (40 mg/m ²) Adjuvant DDP/5FU	2 years	91.9 98*	78.7 86.5*	72.5 84.6*	79.7 89.8*
Lee et al (40)	348	Tx N2-3M0 (UICC 1997)	II-III	2.3 years	RT alone (≥66 Gy, parapharyngeal boost in ~30%) Concurrent CRT (DDP 100 mg/m ² q3 wk) Adjuvant DDP/5FU	3 years	82 92*	73 76	61 70	78 78

WHO, World Health Organization; LRC, Locoregional control; DMFS, Distant metastasis free survival; PFS, Progression-free survival; OS, Overall survival; DDP, Cisplatin (diammine-dichloroplatinum); 5FU, 5-Fluorouracil; UICC, International Union against Cancer Criteria.

*A statistically significant difference.

**A subgroup analysis demonstrated a statistically significant difference in PFS and OS for T3/T4 but not for T1/T2.

underwent laryngectomy followed by adjuvant RT. Concurrent CRT was cisplatin 100 mg on days 1, 22, and 43 of RT. Neck dissection was performed in those patients with a single lymph node 3 cm or greater in diameter or multiple lymph node metastases; laryngectomy was performed on patients with histologically proven persistent or recurrent cancer.

The primary end point was larynx preservation. Secondary end points included overall survival, disease-free survival, locoregional control, time to distant metastases, and laryngectomy-free survival. A total of 547 patients with previously untreated stage III or IV squamous cell carcinoma of the glottic or supraglottic larynx were randomly assigned to 1 of the 3 treatment arms. With a median follow-up of 3.8 years, there was a significantly better rate of laryngeal preservation among the concurrent CRT arm (84%) than that with the IC arm (72%) and the RT-alone arm (67%). Two-year and 5-year overall survival estimates did not differ significantly by treatment. The rate of local control was better for the concurrent CRT group (80%) than that for the IC and RT alone groups (64% and 58%, respectively).

In a follow-up presentation by the investigators (46) after a median of 6.9 years, the 5-year rate of larynx preservation continued to be better in the concurrent CRT arm (83.6%) than that in the IC arm or the RT arm (70.5% and 65.7%, respectively). Locoregional control was significantly better for the concurrent CRT arm (68.8%) than that for the IC arm or RT arm (54.9% and 51%, respectively). In regard to laryngectomy-free survival, rates were similar for the concurrent CRT arm and the IC arm (46.6% and 44.6%, respectively), which were both superior to RT alone (33.9%). Overall survival was similar at 5 years among all 3 treatment arms. The rate of distant metastases was low (14.3% for IC, 13.2% for CRT, and 22.3% for RT alone), with a trend toward benefit from the addition of chemotherapy ($P = .06$).

Overall, the RTOG 91-11 study established definitive CRT as the alternative to total

laryngectomy for patients with advanced laryngeal SCC. However, only 10% of the patients in this study had T4 tumors, and the study excluded patients with large-volume T4 disease, including those with cartilage invasion or extension into the base of tongue of more than 1 cm. Therefore, for such patients, total laryngectomy is still considered the standard of care.

At the University of Michigan, the clinical response to a single cycle of IC is used to select patients with locally advanced laryngeal cancer for subsequent CRT (47). This strategy is offered to patients with stage III or IV laryngeal cancer, including those with large-volume T4 tumors with cartilage invasion or extralaryngeal spread, excluding only patients with severely compromised pretreatment laryngeal function. Patients who achieve a partial response ($>50\%$) after 1 cycle of IC go on to receive CRT, whereas nonresponders undergo immediate surgery with postoperative RT. A retrospective analysis of the outcomes of T4 patients treated by this “chemoselection” approach showed a 3-year overall survival of 78% and laryngectomy-free survival of 65% at 3 years (48). These results strongly support the use of chemoselection as an organ preservation strategy in patients with high-volume T4 tumors with cartilage invasion or extralaryngeal spread and may be considered as an alternative to upfront total laryngectomy in these patients.

Oral Cavity

Most randomized clinical trials of concurrent CRT have not enrolled significant numbers of patients with primary oral cavity tumors or even excluded them from enrollment. This is due to an expectation, right or wrong, of inferior outcome with CRT compared with surgery in oral cavity cancer, secondary to ineffectiveness of RT or unacceptable toxicity. Therefore, most resectable oral cavity cancers are managed with primary surgery, followed by CRT in high-risk cases (See “Adjuvant Concurrent CRT” below).

In a retrospective study from the University of Chicago, data of 111 patients with advanced oral cavity tumors treated with primary concurrent CRT were analyzed (49). Patients were treated with various regimens of intensive concurrent CRT, with or without IC. An encouraging overall survival of 70% at 3 years was found, but toxicity was considerable, including 7.2% treatment-related mortality and osteoradionecrosis rate of 18%. Although the authors concluded that primary CRT should be a viable treatment option for advanced oral cavity cancers, this has not been widely accepted and primary surgery continues to be the mainstay of treatment for these patients.

■ ADJUVANT CONCURRENT CRT

Adjuvant, or postoperative, CRT has been investigated in 2 large randomized trials: EORTC, the European Organization for the Research and Treatment of Cancer 22931 trial (9), and the RTOG, the Radiation Therapy Oncology Group 9501 trial (50).

EORTC

The EORTC 22931 trial (9) compared concomitant cisplatin and RT with RT alone for treatment of operable, advanced head and neck cancer. In this study, 167 patients with previously untreated and operable stage III or IV head and neck cancer from the oral cavity, oropharynx, hypopharynx, or larynx were included. Also included were patients with stage I or II disease with high-risk pathological features, such as extranodal spread, positive resection margins, perineural involvement, and vascular tumor emboli, or patients with oral cavity or oropharyngeal tumors with level IV or V lymph node involvement.

All patients underwent primary surgical resection and received postoperative RT with fractionated doses of 2 Gy each in 5 weekly sessions. The primary site and draining lymphatic region

received up to 54 Gy over 5.5 weeks, and those at risk for dissemination or who had inadequate resection margins received a total of 66 Gy in 33 fractions over 6.5 weeks. Those in the concomitant CRT study arm received cisplatin 100 mg/m² on days 1, 22, and 43 of RT.

The primary end point was progression-free survival. Secondary end points were overall survival, locoregional recurrence, distant metastases, and second primary tumors. With a median follow-up of 60 months, the 5-year progression-free survival rates were 47% for the concurrent CRT group and 36% in the RT only group ($P = .04$). Overall survival favored the concurrent CRT group, with a median survival of 72 months compared to 32 months in the RT alone group. The estimated 5-year cumulative incidence of locoregional recurrence was 18% in the concurrent CRT group and 31% in the RT group ($P = .007$). There was no significant difference in distant metastases or second primary tumors between the 2 groups.

Although this study further supports the use of concurrent CRT in the treatment of advanced head and neck cancer over RT alone, it did not distinguish treatment by anatomic site, and all patients had high-risk pathological and clinical factors. However, it demonstrated that overall survival and locoregional control are improved with the addition of cisplatin to RT treatment regimens.

RTOG

In this study (50), 459 patients with advanced-stage squamous cell carcinoma of the oropharynx, oral cavity, hypopharynx, or larynx were randomly assigned to receive postoperative concurrent cisplatin and RT or RT alone following surgical resection with curative intent. All patients had SCC with high-risk characteristics, such as histologic evidence of invasion of 2 or more regional lymph nodes, extracapsular extension, or microscopically positive margins of resection. All patients underwent postoperative RT in the form of 60 Gy in 30 fractions over a 6-week period, with or without

a 6-Gy boost in 3 fractions to high-risk areas. Those in the concomitant CRT arm received cisplatin 100 mg/m² on days 1, 22, and 43 of RT. The primary end point was locoregional control; secondary end points were disease-free survival, overall survival, and adverse effects.

After a median follow-up of 45.9 months, the rate of locoregional control at 2 years was 72% in the RT alone group and 82% in the concurrent CRT group ($P = .01$). Disease-free survival was significantly better in the concurrent CRT group than that in the RT alone group ($P = .04$); however, overall survival did not differ significantly between the two. A significantly greater number of adverse effects occurred in the concomitant CRT group than that in the RT alone group ($P < .001$).

EORTC Versus RTOG

After the publication of these 2 large studies from Europe (EORTC) and the United States (RTOG), a comparative analysis was performed by Bernier and colleagues to determine the most appropriate subgroup of head and neck cancer patients who would benefit from adjuvant concurrent CRT (51). In their retrospective comparative subgroup analysis, they found that microscopically involved resection margins and extracapsular spread of the tumor from neck nodes are the most significant prognosticators of poor outcome among locally advanced head and neck cancer patients.

In general, both EORTC and RTOG were similar in their treatment arms, but their primary end points and their definition of high risk differed. The primary end points were progression-free survival and locoregional control in the EORTC and RTOG studies, respectively. Both studies considered positive surgical margins and extracapsular extension as high-risk features. High-risk features in the EORTC trial also included lymph node involvement at levels IV or V in oral cavity or oropharyngeal cancer, whereas the RTOG trial included the involvement of 2 or more lymph nodes as a high-risk feature.

Both trials found that locoregional control (EORTC: $P = .007$; RTOG: $P = .011$) and

disease-free survival ($P = .04$ in both trials) were better in the concurrent CRT group than those in RT alone. However, the EORTC trial also found a benefit to overall survival ($P = .02$) in the concurrent CRT group, whereas the RTOG study did not ($P = .19$). As for high-risk features, patients with extracapsular extension and/or positive surgical margins had poorer overall survival rates than those patients without those risk factors in both trials.

■ ALTERED FRACTIONATION RADIATION THERAPY

Altered fractionation RT regimens have been used in the treatment of advanced head and neck cancer in an attempt to improve the therapeutic ratio of RT. A once-daily dose of 1.8 to 2 Gy is considered as standard fractionation. In head and neck cancer, a total dose of 70 Gy given in 35 daily fractions over 7 weeks is considered to be the standard regimen for definitive RT. With accelerated fractionation, the same dose is given in a shorter overall treatment time, thus minimizing tumor repopulation between fractions and increasing tumor control probability for a similar total dose. In hyperfractionated regimens, 2 or 3 fractions are given daily with a reduced dose per fraction. The lower dose per fraction preferentially spares late-responding normal tissues (15) and thereby allows the total dose to be increased, theoretically resulting in a better tumor control probability without an increase in late toxicity. Acceleration and hyperfractionation are often combined (52–57).

Randomized trials of altered fractionation RT have demonstrated an improved locoregional control compared with standard fractionation treatment although no benefit in survival was generally detected (46–50). The use of altered fractionation was associated with increased acute toxicity, especially mucositis, whereas late toxicity was reported to be not significantly different from that of standard RT. A meta-analysis of 15

randomized trials comparing altered fractionated RT with conventional RT concluded that altered fractionation improved 5-year local control by 6.4% and 5-year overall survival by 3.4% (4). The benefit was significantly higher with hyperfractionated RT (absolute benefit of 8% in 5-year survival) than that with accelerated RT (absolute benefit of 2%). This survival benefit is similar in magnitude to the benefit of concurrent CRT in head and neck cancer (3) and led investigators to combine the 2 approaches, altered fractionation and concurrent chemotherapy, in an attempt to further improve local control and survival.

Brizel et al randomized 116 patients with locally advanced head and neck cancer to either hyperfractionated RT alone or the same RT plus concurrent cisplatin and 5-FU (10). Both arms received 2 cycles of adjuvant chemotherapy following RT. Local control was higher in the concurrent chemotherapy arm, but overall survival was not significantly improved. Budach et al (11) reported improved locoregional control and overall survival with the addition of concurrent chemotherapy to altered fractionation RT, with similar toxicities in the 2 arms. However, others reported substantial toxicity with the combination of altered fractionation RT and concurrent chemotherapy (58,59).

Is altered fractionation RT with concurrent chemotherapy better than standard fractionation CRT? The RTOG 0129 addressed this question, with 721 patients randomized to either standard fractionation RT (70 Gy in 35 fractions over 7 weeks) or accelerated concomitant boost RT (72 Gy in 42 fractions over 6 weeks), both with concurrent cisplatin (100 mg/m² every 3 weeks). This trial did not demonstrate any benefit for the accelerated CRT arm over standard fractionation CRT, in terms of overall survival, disease-free survival, locoregional failure, or distant failure (60). Likewise, in another study, presented by Bourhis et al at the 2008 annual meeting of ASTRO, altered fractionation RT with concurrent chemotherapy had no advantage in progression-free survival over standard fractionation CRT (61).

■ TOXICITY OF CRT

The goal of RT is to achieve maximum tumor response with limited injury to surrounding normal tissues and to the patient as a whole. Acute or early radiation toxicity is expressed during or within a few weeks after completion of treatment, typically in tissues and organs with a high cell turnover rate, such as mucosal membranes or the skin. On the other hand, late radiation effects, such as radiation-induced fibrosis, atrophy, neural damage, and vascular damage, may become manifest months to years after therapy and are typically seen in tissues with slow turnover rate. Early radiation toxicity is usually transient, although severe early toxicity may be causally related, at least in part, to subsequent late effects (62). Late radiation toxicity is usually persistent and progressive and may affect the patients' long-term health-related quality of life or even compromise the survival benefit from therapy.

Radiobiologically, the sparing of normal tissues by fractionation is attributed to the recovery of cells from damage between fractions (15). Mechanisms of radiosensitization such as DNA repair inhibition or inhibition of repopulation are not tumor specific and as such they also affect normal tissues within the radiation field. Indeed, concurrent CRT trials for head and neck cancer consistently reported an increased incidence of acute grade 3 and 4 toxic effects compared with radiation alone, with mucositis and skin reaction being the most prevalent.

Acute mucositis is the dose-limiting toxicity of RT for head and neck cancer and is the most common cause of treatment interruptions. Concurrent CRT is associated with increased rates and more severe grades of mucositis compared with RT alone. The mucositis associated with CRT also occurs earlier during treatment and lasts longer than that associated with RT alone. The reported rates of mucositis with concurrent CRT vary considerably among studies, from as low as 25% to higher than 80% (46, 63–67). This, in part, reflects a wide variation in the methods of capturing, grading, and reporting toxicity rather than a real difference (68). In most studies, however, about two-thirds of

the patients are reported to have severe mucositis during concurrent CRT (69). About one-third of patients in earlier concurrent CRT trials were unable to complete their planned chemotherapy due to toxicity (12,70). Unplanned radiation treatment interruptions were also more frequent and of longer duration with concurrent CRT compared with radiation alone.

Other acute toxic effects that are more common with CRT than those with RT alone include nausea and vomiting as well as bone marrow suppression.

Weight loss can serve as a surrogate for global toxicity. In a Swiss study, 30% of the patients receiving concurrent CRT experienced a weight loss of more than 10% compared with only 10% of the patients who received radiation alone (65).

Many early studies concluded that late toxicity was not significantly increased with the addition of concurrent chemotherapy to radiation. However, longer follow-up and phase IV studies suggest that combined CRT does enhance late toxicity (71–74). Xerostomia and swallowing dysfunction with related recurrent aspirations or feeding tube dependence are the most common adverse late effects of head and neck RT, with a profound impact on quality of life. The prevalence of swallowing dysfunction ranges from 30% to 100% depending on the methodology used and is higher in CRT than that with RT alone (71–74). In a multivariate analysis of 3 RTOG trials, 43% of assessable patients had severe late laryngopharyngeal dysfunction after CRT. The most significant variables for severe late toxicity were older age, advanced T-stage, larynx/hypopharynx primary sites, and neck dissection after CRT (74).

Sensorineural hearing loss is another potential late sequel of head and neck RT that involves radiation at a significant dose to the inner ear. The risk of hearing loss seems to be substantially increased after cisplatin-based concurrent CRT (75,76).

Treatment-related death should not be underestimated. In the above-mentioned RTOG analysis, 22 potential treatment-related deaths were reported out of 230 assessable patients (74). In another analysis, 15% of deaths after concurrent CRT were

related to treatment complications, which made it the third cause of death after disease progression and comorbidities (77).

The use of more precise RT techniques, such as IMRT, may reduce the incidence and severity of both acute and late radiation toxicity. Partial sparing of the parotid glands by IMRT has been reported to result in partial preservation of salivary flows, which improve even further over time (78–85). This has translated into improved patient-reported xerostomia and quality of life, although not in all studies (86). Reducing the doses to the noninvolved oral cavity, striving to spare the minor salivary glands, may further improve xerostomia, as well as reduce and limit the extent of acute mucositis. Reducing the dose to swallowing structures, such as the pharyngeal constrictors, is another goal of IMRT, and may improve late dysphagia and aspirations following CRT (87). Additional objectives include reduced doses to the optic pathways and inner ears in patients treated for advanced stage nasopharyngeal and paranasal sinus cancers, and to the skin.

■ EVOLVING PARADIGMS/FUTURE DIRECTIONS

While concurrent CRT improves locoregional control and overall survival over RT alone, its effect on distant metastases is negligible. The addition of IC to concurrent CRT may further improve overall survival by better controlling distant disease. Trials of IC have shown promise in that respect, especially with the use of intensive taxane-based regimens as compared to less intense induction regimens (88–90). However, 2 large studies, the DeCIDE and PARADIGM trials, are designed to test the benefit of IC followed by concurrent CRT as compared to concurrent CRT alone. These studies are still ongoing and their results will hopefully define the role of IC. Sequential chemotherapy followed by concurrent CRT is being investigated in the postoperative setting as well. A phase II study of early postoperative chemotherapy followed by concurrent CRT

for patients with resected high-risk head and neck cancer has shown promising results (91).

The addition of biologic agents to concurrent CRT regimens is another evolving direction. A single phase III study has demonstrated an overall survival benefit for the use of cetuximab, an anti-EGFR antibody, concurrently with radiation as compared to radiation alone in advanced head and neck cancer (92,94). Combining cetuximab with platinum-based chemotherapy has been shown to modestly improve overall survival in recurrent or metastatic head and neck cancer (95), and is currently being investigated in various settings.

An accurate assessment of risk levels using new molecular prognostic markers may improve patients' selection for treatment or even guide individualized therapy. As an example, in recent years HPV-positive oropharyngeal cancers have been found to form a distinct entity with a more favorable clinical course and outcome compared to HPV-negative oropharyngeal cancers (96). It is possible that patients with HPV-positive tumors may benefit from a less intense therapy that will spare them unnecessary toxicity. Future studies, based on tumor HPV status, will have to address this question. In addition, any clinical trial including oropharyngeal cancer patients should include HPV status as a stratification factor.

Further improvements in the therapeutic ratio of combined CRT could possibly be obtained by higher degree of precision in the planning and delivery of RT on one hand and the use of more selective, tumor-specific radiosensitizers, on the other. To that end, a better understanding of drug-radiation interaction in both tumor and normal tissues is needed.

■ KEY POINTS

- Advanced head and neck cancer should be managed by a multidisciplinary team including specialists in head and neck surgery, radiation oncology, and medical oncology.
- Treatment should be individualized according to the primary tumor site, tumor stage, specific clinical and pathological features, as well as patient-related factors such as age, performance status, comorbidities, and personal preferences.
- Concurrent chemoradiotherapy for advanced head and neck cancer results in an absolute survival benefit of 6.5% at 5 years compared with radiation alone. This benefit is mainly attributed to improved locoregional control, with a small effect, if any, on distant metastases.
- Concurrent chemoradiotherapy is the standard of care for locally advanced head and neck cancers and has allowed organ preservation in the majority of patients with oropharyngeal and laryngeal cancers. Surgery is mainly reserved for salvage.
- Postoperative chemoradiotherapy is superior to radiotherapy alone in patients with resected high-risk tumors.
- Induction chemotherapy has a modest effect on survival; however, ongoing studies are expected to define its role.
- Acute and late toxicities associated with concurrent chemoradiotherapy are considerable.
- Advances in radiation therapy may reduce the incidence and severity of both acute and late radiation toxicity.
- The use of more targeted, tumor-selective radiosensitizers is expected to further improve the therapeutic ratio of chemoradiotherapy and allow better organ and function preservation.

■ REFERENCES

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. *CA Cancer J Clin.* 2009;59: 225–249.
2. Sturgis EM, Cinciripini PM. Trends in head and neck cancer incidence in relation to smoking prevalence: an emerging epidemic of human papillomavirus-associated cancers? *Cancer.* 2007;110:1429–1435.
3. Pignon JP, le Maitre A, Maillard E, Bourhis J; MACH-NC Collaborative Group. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC):

- an update on 93 randomised trials and 17,346 patients. *Radiother Oncol.* 2009;92:4–14.
4. Bourhis J, Overgaard J, Audry H, et al. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. *Lancet* 2006;368:843–854.
 5. Steel GG. Terminology in the description of drug-radiation interactions. *Int J Radiat Oncol Biol Phys.* 1979;5:1145–1150.
 6. Steel GG. The search for therapeutic gain in the combination of radiotherapy and chemotherapy. *Radiother Oncol.* 1988;11:31–53.
 7. Adelstein DJ, Li Y, Adams GL, et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. *J Clin Oncol.* 2003;21:2–98.
 8. Denis F, Garaud P, Bardet E, et al. Final results of the 94-01 French Head and Neck Oncology and Radiotherapy Group randomized trial comparing radiotherapy alone with concomitant radiochemotherapy in advanced-stage oropharynx carcinoma. *J Clin Oncol.* 2004;22:69–76.
 9. Bernier J, Dommene C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med.* 2004;350:1945–1952.
 10. Brizel DM, Albers ME, Fisher SR, et al. Hyperfractionated irradiation with or without concurrent chemotherapy for locally advanced head and neck cancer. *N Engl J Med.* 1998;338:1798–1804.
 11. Budach V, Stuschke M, Budach W, et al. Hyperfractionated accelerated chemoradiation with concurrent fluorouracil-mitomycin is more effective than dose-escalated hyperfractionated accelerated radiation therapy alone in locally advanced head and neck cancer: final results of the radiotherapy cooperative clinical trials group of the German Cancer Society 95-06 Prospective Randomized Trial. *J Clin Oncol.* 2005;23:1125–1135.
 12. Al-Sarraf M, LeBlanc M, Giri PG, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. *J Clin Oncol.* 1998;16:1310–1317.
 13. Wee J, Tan EH, Tai BC, et al. Randomized trial of radiotherapy versus concurrent chemoradiotherapy followed by adjuvant chemotherapy in patients with American Joint Committee on Cancer/International Union against cancer stage III and IV nasopharyngeal cancer of the endemic variety. *J Clin Oncol.* 2005;23:6730–6738.
 14. Seiwert TY, Salama JK, Vokes EE. The concurrent chemoradiation paradigm—general principles. *Nat Clin Pract Oncol.* 2007;4:86–100.
 15. Willers H, Held KD. Introduction to clinical radiation biology. *Hematol Oncol Clin North Am.* 2006;20:1–24.
 16. Begg AC. Cisplatin and radiation: interaction probabilities and therapeutic possibilities. *Int J Radiat Oncol Biol Phys.* 1990;19:1183–1189.
 17. Yang LX, Douple EB, O'Hara JA, Wang HJ. Production of DNA double-strand breaks by interactions between carboplatin and radiation: a potential mechanism for radiopotential. *Radiat Res.* 1995;143:309–315.
 18. Yang LX, Douple E, Wang HJ. Irradiation-enhanced binding of carboplatin to DNA. *Int J Radiat Biol.* 1995;68:609–614.
 19. Yang LX, Douple EB, O'Hara JA, Wang HJ. Carboplatin enhances the production and persistence of radiation-induced DNA single-strand breaks. *Radiat Res.* 1995;143:302–308.
 20. Richmond RC, Khokhar AR, Teicher BA, Douple EB. Toxic variability and radiation sensitization by Pt(II) analogs in *Salmonella typhimurium* cells. *Radiat Res.* 1984;99:609–626.
 21. Myint WK, Ng C, Raaphorst GP. Examining the non-homologous repair process following cisplatin and radiation treatments. *Int J Radiat Biol.* 2002;78:417–424.
 22. Dolling JA, Boreham DR, Brown DL, Raaphorst GP, Mitchel RE. Cisplatin-modification of DNA repair and ionizing radiation lethality in yeast, *Saccharomyces cerevisiae*. *Mutat Res.* 1999;433:127–136.
 23. Turchi JJ, Henkels KM, Zhou Y. Cisplatin-DNA adducts inhibit translocation of the Ku subunits of DNA-PK. *Nucleic Acids Res.* 2000;28:4634–4641.
 24. Shewach DS, Lawrence TS. Antimetabolite radiosensitizers. *J Clin Oncol.* 2007;25:4043–4050.
 25. Bruso CE, Shewach DS, Lawrence TS. Fluorodeoxyuridine-induced radiosensitization and inhibition of DNA double strand break repair in human colon cancer cells. *Int J Radiat Oncol Biol Phys.* 1990;19:1411–1417.
 26. Shewach DS, Hahn TM, Chang E, Hertel LW, Lawrence TS. Metabolism of 2',2'-difluoro-2'-deoxycytidine and radiation sensitization of human colon carcinoma cells. *Cancer Res.* 1994;54:3218–3223.
 27. Latz D, Fleckenstein K, Eble M, Blatter J, Wannenmacher M, Weber KJ. Radiosensitizing potential of gemcitabine (2',2'-difluoro-2'-deoxycytidine) within the cell cycle in vitro. *Int J Radiat Oncol Biol Phys.* 1998;41:875–882.
 28. Eisbruch A, Shewach DS, Bradford CR, et al. Radiation concurrent with gemcitabine for locally advanced head and neck cancer: a phase I trial and intracellular drug incorporation study. *J Clin Oncol.* 2001;19:792–799.

29. Tishler RB, Geard CR, Hall EJ, Schiff PB. Taxol sensitizes human astrocytoma cells to radiation. *Cancer Res.* 1992;52:3495–3497.
30. Hei TK, Piao CQ, Geard CR, Hall EJ. Taxol and ionizing radiation: interaction and mechanisms. *Int J Radiat Oncol Biol Phys.* 1994;29:267–271.
31. Geard CR, Jones JM. Radiation and taxol effects on synchronized human cervical carcinoma cells. *Int J Radiat Oncol Biol Phys.* 1994;29:565–569.
32. Kim JJ, Tannock IF. Repopulation of cancer cells during therapy: an important cause of treatment failure. *Nat Rev Cancer.* 2005;5:516–525.
33. Krause M, Ostermann G, Petersen C, et al. Decreased repopulation as well as increased reoxygenation contribute to the improvement in local control after targeting of the EGFR by C225 during fractionated irradiation. *Radiother Oncol.* 2005;76:162–167.
34. Feng FY, Lopez CA, Normolle DP, et al. Effect of epidermal growth factor receptor inhibitor class in the treatment of head and neck cancer with concurrent radiochemotherapy in vivo. *Clin Cancer Res.* 2007;13:2512–2518.
35. Soo KC, Tan EH, Wee J, et al. Surgery and adjuvant radiotherapy vs concurrent chemoradiotherapy in stage III/IV nonmetastatic squamous cell head and neck cancer: a randomised comparison. *Br J Cancer.* 2005;93:279–286.
36. Al-Sarraf M, LeBlanc M, Giri PGS, et al. Superiority of five year survival with chemoradiotherapy (CT-RT) vs radiotherapy in patients (pts) with locally advanced nasopharyngeal cancer (NPC). Intergroup (0099) (SWOG 8892, RTOG 8817, ECOG 2388) Phase III study: final report. Presented at the 37th Annual Meeting of the American Society of Clinical Oncology; May 12–15, 2001; San Francisco. Abstract.
37. Chan AT, Leung SF, Ngan RK, et al. Overall survival after concurrent cisplatin-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma. *J Natl Cancer Inst.* 2005;97:536–539.
38. Lin JC, Jan JS, Hsu CY, Liang WM, Jiang RS, Wang WY. Phase III study of concurrent chemoradiotherapy versus radiotherapy alone for advanced nasopharyngeal carcinoma: positive effect on overall and progression-free survival. *J Clin Oncol.* 2003;21:631–637.
39. Chen Y, Liu MZ, Liang SB, et al. Preliminary results of a prospective randomized trial comparing concurrent chemoradiotherapy plus adjuvant chemotherapy with radiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma in endemic regions of china. *Int J Radiat Oncol Biol Phys.* 2008;71:1356–1364. (40. Lee JCO 2005)
40. Baujat B, Audry H, Bourhis J, et al. Chemotherapy in locally advanced nasopharyngeal carcinoma: an individual patient data meta-analysis of eight randomized trials and 1753 patients. *Int J Radiat Oncol Biol Phys.* 2006;64:47–56.
41. Langendijk JA, Leemans CR, Buter J, Berkhof J, Slotman BJ. The additional value of chemotherapy to radiotherapy in locally advanced nasopharyngeal carcinoma: a meta-analysis of the published literature. *J Clin Oncol.* 2004;22:4604–4612.
42. Hui EP, Ma BB, Leung SF, et al. Randomized phase II trial of concurrent cisplatin-radiotherapy with or without neoadjuvant docetaxel and cisplatin in advanced nasopharyngeal carcinoma. *J Clin Oncol.* 2009;27:242–249.
43. DeSanto LW. T3 glottic cancer: options and consequences of the options. *Laryngoscope.* 1984;94:1311–1315.
44. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. The Department of Veterans Affairs Laryngeal Cancer Study Group. *N Engl J Med.* 1991;324:1685–1690.
45. Forastiere AA, Goepfert H, Maor M, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *N Engl J Med.* 2003;349:2091–2098.
46. Forastiere AA, Maor M, Weber RS, et al. Long-term results of Intergroup RTOG 91-11: A phase III trial to preserve the larynx—Induction cisplatin/5-FU and radiation therapy versus concurrent cisplatin and radiation therapy versus radiation therapy. Presented at the 42nd Annual Meeting of the American Society of Clinical Oncology; June 2–6, 2006; Atlanta. Abstract.
47. Urba S, Wolf G, Eisbruch A, et al. Single-cycle induction chemotherapy selects patients with advanced laryngeal cancer for combined chemoradiation: a new treatment paradigm. *J Clin Oncol.* 2006;24:593–598.
48. Worden FP, Moyer J, Lee JS, et al. Chemoselection as a strategy for organ preservation in patients with T4 laryngeal squamous cell carcinoma with cartilage invasion. *Laryngoscope.* 2009;119:1510–1517.
49. Stenson KM, Kunnavakkam R, Cohen EE, et al. Chemoradiation for patients with advanced oral cavity cancer. *Laryngoscope.* 2010;120:93–99.
50. Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *N Engl J Med.* 2004;350:1937–1944.
51. Bernier J, Cooper JS, Pajak TF, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation

- plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). *Head Neck*. 2005;27:843–850.
52. Fu KK, Pajak TF, Trotti A, et al. A Radiation Therapy Oncology Group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: first report of RTOG 9003. *Int J Radiat Oncol Biol Phys*. 2000;48:7–16.
 53. Horiot JC, Le Fur R, N'Guyen T, et al. Hyperfractionation versus conventional fractionation in oropharyngeal carcinoma: final analysis of a randomized trial of the EORTC cooperative group of radiotherapy. *Radiother Oncol*. 1992;25:231–241.
 54. Pinto LH, Canary PC, Araujo CM, Bacelar SC, Souhami L. Prospective randomized trial comparing hyperfractionated versus conventional radiotherapy in stages III and IV oropharyngeal carcinoma. *Int J Radiat Oncol Biol Phys*. 1991;21:557–562.
 55. Overgaard J, Hansen HS, Specht L, et al. Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck: DAHANCA 6 and 7 randomised controlled trial. *Lancet*. 2003;362:933–940.
 56. Bourhis J, Lapeyre M, Tortochaux J, et al. Phase III randomized trial of very accelerated radiation therapy compared with conventional radiation therapy in squamous cell head and neck cancer: a GORTEC trial. *J Clin Oncol*. 2006;24:2873–2878.
 57. Kasibhatla M, Prosnitz LR, Fisher SR, et al. Hyperfractionated radiotherapy versus hyperfractionated radiotherapy and concomitant chemotherapy in locally advanced head and neck cancer. Presented at the 49th Annual Meeting of the American Society for Therapeutic Oncology and Radiology; October 28–November 1, 2007; Los Angeles. Abstract.
 58. Staar S, Rudat V, Stuetzer H, et al. Intensified hyperfractionated accelerated radiotherapy limits the additional benefit of simultaneous chemotherapy—results of a multicentric randomized German trial in advanced head-and-neck cancer. *Int J Radiat Oncol Biol Phys*. 2001;50:1161–1171.
 59. Garden AS, Harris J, Trotti A, et al. Long-term results of concomitant boost radiation plus concurrent cisplatin for advanced head and neck carcinomas: a phase II trial of the radiation therapy oncology group (RTOG 99-14). *Int J Radiat Oncol Biol Phys*. 2008;71:1351–1355.
 60. Ang K, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. 2010;363:24–35.
 61. Bourhis J, Sire C, Lapeyre M et al. Accelerated versus conventional radiotherapy with concomitant chemotherapy in locally advanced head and neck carcinomas: results of phase III randomized trial. Presented at the 50th Annual Meeting of the American Society for Therapeutic Oncology and Radiology; September 21–25, 2008; Boston. Abstract.
 62. Dorr W, Hendry JH. Consequential late effects in normal tissues. *Radiother Oncol*. 2001;61:223–231.
 63. Hao D, Ritter MA, Oliver T, Browman GP. Platinum-based concurrent chemoradiotherapy for tumors of the head and neck and the esophagus. *Semin Radiat Oncol*. 2006;16:10–19.
 64. Bieri S, Bentzen SM, Huguenin P, et al. Early morbidity after radiotherapy with or without chemotherapy in advanced head and neck cancer. Experience from four nonrandomized studies. *Strahlenther Onkol*. 2003;179:390–395.
 65. Lee NY, O'Meara W, Chan K, et al. Concurrent chemotherapy and intensity-modulated radiotherapy for locoregionally advanced laryngeal and hypopharyngeal cancers. *Int J Radiat Oncol Biol Phys*. 2007;69:459–468.
 66. Trotti A, Garden A, Warde P, et al. A multinational, randomized phase III trial of iseganan HCl oral solution for reducing the severity of oral mucositis in patients receiving radiotherapy for head-and-neck malignancy. *Int J Radiat Oncol Biol Phys*. 2004;58:674–681.
 67. Bentzen SM, Trotti A. Evaluation of early and late toxicities in chemoradiation trials. *J Clin Oncol*. 2007;25:4096–4103.
 68. Bernier J. Current state-of-the-art for concurrent chemoradiation. *Semin Radiat Oncol*. 2009;19:3–10.
 69. Calais G, Alfonsi M, Bardet E, et al. Randomized trial of radiation therapy versus concomitant chemotherapy and radiation therapy for advanced-stage oropharynx carcinoma. *J Natl Cancer Inst*. 1999;91:2081–2086.
 70. Nguyen NP, Moltz CC, Frank C, et al. Dysphagia following chemoradiation for locally advanced head and neck cancer. *Ann Oncol*. 2004;15:383–388.
 71. Kotz T, Costello R, Li Y, Posner MR. Swallowing dysfunction after chemoradiation for advanced squamous cell carcinoma of the head and neck. *Head Neck*. 2004;26:365–372.
 72. Eisbruch A, Lyden T, Bradford CR, et al. Objective assessment of swallowing dysfunction and aspiration after radiation concurrent with chemotherapy for head-and-neck cancer. *Int J Radiat Oncol Biol Phys*. 2002;53:23–28.
 73. Frowen JJ, Perry AR. Swallowing outcomes after radiotherapy for head and neck cancer: a systematic review. *Head Neck*. 2006;28:932–944.

74. Machtay M, Moughan J, Trotti A, et al. Factors associated with severe late toxicity after concurrent chemoradiation for locally advanced head and neck cancer: an RTOG analysis. *J Clin Oncol*. 2008;26:3582–3589.
75. Low WK, Toh ST, Wee J, Fook-Chong SM, Wang DY. Sensorineural hearing loss after radiotherapy and chemoradiotherapy: a single, blinded, randomized study. *J Clin Oncol*. 2006;24:1904–1909.
76. Chen WC, Jackson A, Budnick AS, et al. Sensorineural hearing loss in combined modality treatment of nasopharyngeal carcinoma. *Cancer*. 2006;106:820–829.
77. Argiris A, Brockstein BE, Haraf DJ, et al. Competing causes of death and second primary tumors in patients with locoregionally advanced head and neck cancer treated with chemoradiotherapy. *Clin Cancer Res*. 2004;10:1956–1962.
78. Eisbruch A. Radiotherapy: IMRT reduces xerostomia and potentially improves QoL. *Nat Rev Clin Oncol*. 2009;6:567–568.
79. Lee N, Xia P, Quivey JM, et al. Intensity-modulated radiotherapy in the treatment of nasopharyngeal carcinoma: an update of the UCSF experience. *Int J Radiat Oncol Biol Phys*. 2002;53:12–22.
80. Kam MK, Leung SF, Zee B, et al. Prospective randomized study of intensity-modulated radiotherapy on salivary gland function in early-stage nasopharyngeal carcinoma patients. *J Clin Oncol*. 2007;25:4873–4879.
81. Pow EH, Kwong DL, McMillan AS, et al. Xerostomia and quality of life after intensity-modulated radiotherapy vs. conventional radiotherapy for early-stage nasopharyngeal carcinoma: initial report on a randomized controlled clinical trial. *Int J Radiat Oncol Biol Phys*. 2006;66:981–991.
82. Lee N, Harris J, Garden AS, et al. Intensity-modulated radiation therapy with or without chemotherapy for nasopharyngeal carcinoma: radiation therapy oncology group phase II trial 0225. *J Clin Oncol*. 2009;27:3684–3690.
83. Nutting C, A'Hern R, Rogers MS, et al. First results of a phase III multicenter randomized controlled trial of intensity modulated (IMRT) versus conventional radiotherapy (RT) in head and neck cancer (PARSPORT: ISRCTN 48243537; CRUK/03/005). Presented at the 45th Annual Meeting of the American Society of Clinical Oncology; May 29–June 2, 2009; Orlando. Abstract.
84. Lin A, Kim HM, Terrell JE, Dawson LA, Ship JA, Eisbruch A. Quality of life after parotid-sparing IMRT for head-and-neck cancer: a prospective longitudinal study. *Int J Radiat Oncol Biol Phys*. 2003;57:61–70.
85. Parliament MB, Scrimger RA, Anderson SG, et al. Preservation of oral health-related quality of life and salivary flow rates after inverse-planned intensity-modulated radiotherapy (IMRT) for head-and-neck cancer. *Int J Radiat Oncol Biol Phys*. 2004;58:663–673.
86. Eisbruch A. Reducing xerostomia by IMRT: what may, and may not, be achieved. *J Clin Oncol*. 2007;25:4863–4864.
87. Feng FY, Kim HM, Lyden TH, et al. Intensity-modulated radiotherapy of head and neck cancer aiming to reduce dysphagia: early dose-effect relationships for the swallowing structures. *Int J Radiat Oncol Biol Phys*. 2007;68:1289–1298.
88. Monnerat C, Faivre S, Temam S, Bourhis J, Raymond E. End points for new agents in induction chemotherapy for locally advanced head and neck cancers. *Ann Oncol*. 2002;13:995–1006.
89. Posner MR, Hershock DM, Blajman CR, et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. *N Engl J Med*. 2007;357:1705–1715.
90. Vermorken JB, Remenar E, van Herpen C, et al. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. *N Engl J Med*. 2007;357:1695–1704.
91. Rosenthal DI, Harris J, Forastiere AA, et al. Early postoperative paclitaxel followed by concurrent paclitaxel and cisplatin with radiation therapy for patients with resected high-risk head and neck squamous cell carcinoma: report of the phase II trial RTOG 0024. *J Clin Oncol*. 2009;27:4727–4732.
92. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med*. 2006;354:567–578.
93. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. *Lancet Oncol*. 2010;11:21–28.
94. Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med*. 2008;359:1116–1127.
95. Haddad RI, Tishler RB, Norris C, et al. Phase I study of C-TPF in patients with locally advanced squamous cell carcinoma of the head and neck. *J Clin Oncol*. 2009;27:4448–4453.
96. Vidal L, Gillison ML. Human papillomavirus in HNSCC: recognition of a distinct disease type. *Hematol Oncol Clin North Am*. 2008;22:1125–1142, vii.

CHAPTER 8

Multidisciplinary Management of Thyroid Cancer

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Thyroid cancer is the most common endocrine malignancy with an estimated 44,670 cases diagnosed in the United States in 2010 (1). In the United States, the incidence of thyroid cancers has risen steadily from the 1970s to 2010. The increasing incidence may be partially explained by increased use of ultrasound and detection of small tumors. There are, however, also data showing that the incidence of larger tumors is on the rise, suggesting that additional factors, such as environmental exposures, may be contributing to the increase in incidence (1–4). Thyroid cancer is more than three times prevalent among women than men. The peak incidence in women is in the early 50s, whereas the peak incidence in men occurs between 60 and 69 years of age. Higher mortality rates are seen in men with thyroid cancer compared to women, which may be due to an older age in men at presentation (5,6).

Thyroid cancer is divided into three major groups: (1) differentiated thyroid cancer (DTC); (2) anaplastic thyroid cancer (ATC); and (3) medullary thyroid cancer (MTC). DTC is the most common and accounts for approximately 93% of all cases of thyroid cancer, with anaplastic and MTCs accounting for approximately 2% and 5%, respectively.

■ DIFFERENTIATED THYROID CANCER

There are two predominant histologic subtypes of DTC, papillary thyroid cancer (PTC), and follicular thyroid cancer (FTC).

Papillary thyroid carcinoma accounts for approximately 85% of DTC. The diagnosis of PTC is frequently made by fine needle aspiration (FNA) of a thyroid nodule. PTC is characterized by papillary structures with fibrovascular cores and epithelial cells containing large pale nuclei (Orphan Annie eyes) with nuclear membrane irregularities and grooves. There are often associated concentric calcifications, psammoma bodies, and invaginations of the pink cytoplasm within nuclei, the so-called pseudoinclusions of PTC (7). PTCs are often multifocal, which can occur due to intraglandular spread or the development of distinct tumor foci with independent clonal origins (8,9). PTC can spread via lymphatics, and generally, regional lymph nodes in the neck are the initial site of metastatic spread.

FTC accounts for approximately 15% of DTC. The diagnosis of FTC requires the presence of capsular and/or vascular invasion. As a consequence, the diagnosis of FTC cannot be made by cytology alone. FTC histology ranges from well-differentiated

epithelium with colloid and follicular development to poorly differentiated solid growth patterns, with marked nuclear atypia and extensive vascular and/or capsular invasion. These latter features are associated with a worse prognosis (7). FTCs can spread hematogenously, thus pulmonary and osseous metastases are often the initial site of recurrence.

Multiple staging systems exist for DTC. The AJCC/UICC TNM staging system is the most widely used and predicts disease-specific mortality (10). Larger tumor size (T), extrathyroidal extension, presence of nodal metastasis, presence of distant metastasis, and age greater than 45 are all associated with a higher stage and worse prognosis. Of note, for patients under 45 years old, the maximum TNM stage is II, which reflects the generally

indolent nature of DTC in younger adults. The MACIS (metastasis, age, completeness of resection, invasion, and size) scoring system assigns a point value for the major variables and computes a score that allows an estimate of disease-specific mortality (11). In addition to these variables, several other clinicopathologic variables appear associated with higher risk disease. These include specific high-risk subtypes of PTC, such as tall cell variant, poorly differentiated tumors, FDG avidity, and lack of uptake of radioiodine (12–21).

There are a variety of genetic alterations that are thought responsible for the development of DTCs. Point mutations and rearrangements play a role in the pathogenesis of all types of thyroid cancer (Table 8.1). Of note is the fact that these genetic

TABLE 8.1
Frequency of molecular alterations in thyroid cancers

Alteration	PTC (%)	FTC (%)	ATC (%)	Sporadic MTC (%)	Hereditary MTC (%)	Comments
<i>BRAF</i> mutation	40–50	0	15–50	—	—	V600E point mutation most common
<i>RET/PTC</i> rearrangement	10–40	0	0	—	—	Particularly common in pediatric cancers (50%–60%) and radiation-related cancers (60%–70%)
<i>RAS</i> mutation	10	40–50	5–50	—	—	Uncommon in PTCs, excepting the follicular variant <i>N-RAS</i> mutations more common than <i>H-RAS</i>
<i>NTRK1</i> rearrangement	5–10	—	—	—	—	Can be seen in post-Chernobyl cancers
<i>PPARG</i> rearrangement	0	25–60	0	—	—	<i>BRAF</i> , <i>RET/PTC</i> , <i>RAS</i> , and <i>PPARG</i> alterations are generally mutually exclusive
<i>CTNNB1</i> mutation	0	0	30–65	—	—	
<i>TP53</i> mutation	<10	<10	55–60		20	
<i>PIK3CA</i> mutation	<5	6–13	12–23	—	—	
<i>RET</i> mutation	—	—	—	25–70	>95	Codon 918 mutations most common in sporadic MTC, codon 634 mutations most common in MEN2A. There is strong genotype-phenotype correlation

alterations occur with little overlap between papillary and follicular carcinomas. In DTC, alterations in genes encoding proteins in the mitogen-activated protein kinase (MAPK) signaling pathway are common. The most frequent mutation in PTC occurs in *BRAF*, which encodes a serine/threonine kinase involved in activation of the MAPK pathway. Point mutations within *BRAF*, the most common of which is the V600E mutation, lead to constitutive activation and downstream phosphorylation of kinases, such as MEK1 and 2, and finally ERK 1 and 2. ERK is responsible for the activity of a number of intranuclear regulatory proteins that play a role in proliferation, differentiation, and survival of follicular cells (20,22). *BRAF* mutations occur in approximately 40% to 50% of PTCs and are associated with older age, lymph node involvement, distant metastasis, decreased uptake of radioactive iodine, and risk of recurrent disease (18,20,23–28).

RET/PTC rearrangements are the second most common genetic abnormality seen in PTC (29,30). *RET* is a protooncogene that encodes a tyrosine kinase. Activation by ligand results in *RET* dimerization and autophosphorylation of its intracellular tyrosine kinase domain. Rearrangements of *RET* with heterologous genes normally expressing follicular cells result in ligand-independent fusion oncoproteins that activate several intracellular signaling pathways involved in proliferation, differentiation, and apoptosis, including the MAPK and phosphatidylinositol-3-kinase (PI3K)/AKT pathways. The prevalence of *RET/PTC* rearrangements varies with geographic region and age and is particularly common in post-Chernobyl thyroid cancer and PTC in young patients (30–35). In the United States, the rate of *RET/PTC* rearrangements in PTC is approximately 35% (30,36–39). Other genetic defects seen in PTC include *RAS* and neurotrophic tyrosine kinase receptor 1 (35,40). In all, approximately 70% of all PTCs will have one of the activating genetic mutations mentioned above (41). Mutations found in FTC tend to be distinct from those common to PTC. For example, *RET* rearrangements and *BRAF* mutations are not characteristic of FTC, whereas *RAS* mutations and *PPARG* rearrangements are

seen in approximately 50% and 35% of FTCs, respectively (42). These molecular changes and others prevalent in thyroid cancer now offer strong rationale behind exploring a number of targeted therapies in advanced disease.

DTC typically carries an excellent prognosis and in most cases can be treated adequately with surgery, frequently followed by radioactive iodine 131 (RAI). The goals of surgery include: (1) to resect the primary tumor, any involved lymph nodes and disease that extends beyond the thyroid capsule; (2) to address the frequent multicentric nature of PTCs; (3) to facilitate subsequent RAI therapy (RAI thyroid remnant ablation or RAI treatment of residual and/or metastatic disease) where appropriate; (4) to allow for follow-up surveillance with RAI scanning and evaluation of serum thyroglobulin levels; and (5) to minimize surgical morbidity (43,44). Patients with tumors greater than 1 cm should undergo total or near-total thyroidectomy, while lobectomy alone may be sufficient for tumors <1 cm; if they are unifocal, there is no history of irradiation to the neck, and there is no evidence of lymph node involvement (43,45–47). Completion thyroidectomy should be offered to patients who have pathological findings that would have resulted in an initial recommendation for total thyroidectomy (43). At centers with high surgical volume, the rates of complications following total thyroidectomy are as low as 0.2% to 0.4% (46–48).

Treatment with radioactive iodine postoperatively is indicated for patients with tumors >4 cm, tumors with gross extrathyroidal extension, or distant metastatic disease. Postoperative RAI has several distinct benefits. These include ablation of distant metastatic disease, ablation of microscopic residual disease, and remnant ablation to facilitate RAI whole-body scanning. Consultation with an endocrinologist or nuclear medicine physician specializing in the treatment of thyroid cancer is recommended to individualize the dosing of RAI, and the regimen for thyroid hormone withdrawal (43,44).

Thyroid stimulating hormone (TSH) is a mitogen for DTC. TSH can be suppressed by

exogenous administration of LT4 (thyroxine). The goals of TSH suppression are to minimize the risk of disease recurrence and morbidity. Individuals at high risk for recurrence are recommended to have TSH suppression to below 0.1 mU/L, while individuals with lower risk cancers may be suppressed to the 0.1 to 0.5 mU/L range. Suppression of TSH can lead to mild thyrotoxicosis with long-term effects including exacerbation of angina, atrial fibrillation, and osteoporosis. TSH suppression should be individualized and closely monitored (43,44).

The role of external beam radiotherapy (EBRT) in the management of DTC is an area of some controversy due to a lack of prospective randomized trials. The purpose of EBRT in DTC is to improve locoregional control in patients at high risk for recurrence. Patients with unresectable disease, gross residual disease following surgery, or disease unlikely to be optimally treated by further surgery or RAI are candidates for EBRT. Because of the lack of prospective study, indications for EBRT in DTC rely upon retrospective data from single institution experiences, such as two recent series reporting on 76 patients receiving EBRT for nonanaplastic thyroid cancer and 131 patients with DTC, respectively (49,50). The most frequent indications for treatment in these series included unresectable disease, gross residual disease following surgery, microscopically positive margins, extrathyroidal extension, and/or extracapsular nodal extension. The locoregional control rates in these studies were 72% and 79%, and the overall survival rates at 4 years were 55% and 73%, respectively. The use of conformal, intensity-modulated radiotherapy (IMRT) is associated with a decrease in radiation-induced side effects (50). The timing of radiation therapy and treatment with RAI should be individualized with a multidisciplinary team.

The 10-year overall survival rates for PTC and FTC are approximately 95% and 90%, respectively (6,51). While these overall survival rates are quite good, approximately 30% of patients with DTC will experience disease recurrence. Recurrent disease can involve the thyroid bed or cervical lymph nodes or the trachea or neck muscles, or can occur distantly,

with metastasis to the lungs and bones seen most commonly. Recurrent nodal disease in the neck can usually be managed with surgery and consideration of additional RAI. In patients with recurrent disease, FDG avidity and iodine uptake can be used to risk stratify patients for survival. Patients with recurrent thyroid cancer who have FDG-avid disease that does not concentrate radioiodine are at the highest risk for death. Thus, a more aggressive treatment approach in these patients should be considered (16,52,53).

Metastatic iodine-refractory DTC poses significant treatment challenges, though recent developments are bringing about major improvements in the field. For years, cytotoxic chemotherapy was the only treatment alternative for these patients. Doxorubicin, alone or in combination, has been the best studied chemotherapy for DTC. An early study of the drug in the 1970s suggested some activity, with a response rate of 37% (54). However, subsequent studies of doxorubicin monotherapy and combination chemotherapy carried out in small numbers of patients showed lower response rates (55–59). Cytotoxic chemotherapy's low level of activity, coupled with its toxicities, makes this approach difficult to justify in many patients with DTC, particularly those with slowly progressive disease.

On the other hand, a number of clinical trials examining targeted therapies in DTC have been completed in the last several years, and a number of other studies are currently underway. Small-molecule tyrosine kinase inhibitors (TKIs) have shown the most promise. Motesanib, a multikinase inhibitor targeting VEGFR-1, 2, and 3, Kit, RET, and PDGFR, was the first in its class to demonstrate activity in iodine-refractory DTC (60). In a multicenter, international, phase II trial, 93 patients with progressive disease within the prior 6 months were treated with motesanib. The objective response rate was 14%, and 35% of patients had stable disease lasting at least 24 weeks. Median progression-free survival (PFS) was 40 weeks. Similar to slightly more impressive response rates and PFS have been seen in other TKIs, namely axitinib, sorafenib, sunitinib, and pazopanib (61–67). Comparing results across

these phase II studies is difficult, particularly because entry criteria vary from study to study, leading to heterogeneity in the cohorts studied. Despite this variability, the studies demonstrate a consistent response for patients with iodine-refractory thyroid cancer treated with VEGFR inhibitors. TKIs, which have anti-VEGFR2 activity, appear to offer clinical benefit for 40% to 60% of patients treated for a duration of 12 to 24 months. Side effects include hypertension, proteinuria, fatigue, diarrhea, rash, bone marrow suppression, and rare side effects such as ventricular dysfunction, thromboembolism, bleeding, and wound healing complications. Since many patients with metastatic thyroid cancer have slow-growing disease that can be asymptomatic for many years, the timing of therapy must be individualized to each patient.

Multiple challenges exist in optimizing the clinical development of targeted therapy for thyroid cancer patients. Defining the histologic and molecular subtypes most likely to respond to therapy is a clear priority. Phase II studies performed to date have demonstrated responses in the major histologic subtypes of DTC. *BRAF* mutational status has not been shown to be predictive of response. The VEGFR TKIs may also exert their effect on tumor stroma, so it is unclear if there are stromal factors that may influence response. Identifying the clinical, pathological, and molecular determinants of response to therapy is a key challenge for the future.

Current and future efforts to expand treatment options for patients with advanced iodine-refractory DTC beyond VEGFR TKIs include the exploration of other targeted therapies and other methods for targeting angiogenesis, such as blockade with VEGF-Trap or combined VEGFR antagonism. Other targets of interest for which there are now potentially effective agents in the development pipeline include *BRAF*, *RAS*, *RET*, and the PIK-3/AKT/mammalian target of rapamycin (mTOR) pathway. Rationale for combination targeted therapy in DTC is also now emerging. For example, thyroid cancers can exhibit activation of more than one signaling pathway, such as activation of the *ras*/RAF/MEK

and PI-3K/AKT/mTOR pathways. When multiple growth and survival pathways are upregulated in a given tumor, a compelling argument can be made for enhancing efficacy by targeting multiple pathways. In preclinical models, this has been shown to be the case, with combined administration of the MEK inhibitor, AZD6244, plus rapamycin leading to enhanced growth inhibition in thyroid cancer cell lines in vitro and in xenografted tumors (68). Lastly, there has long been interest in redifferentiation of advanced thyroid cancers, based upon the well-characterized phenomenon of thyroid cancer dedifferentiation, which results in downregulation of the sodium iodide symporter (NIS) that is essential for the active transport of iodine into follicular cells. Loss of NIS, as seen in *BRAF* mutant tumors, impairs the ability of the tumor cells to concentrate radioiodine, making them refractory to RAI. In thyroid cancer cell lines, several agents have shown the ability to increase NIS expression, including retinoic acid, rosiglitazone, and histone deacetylase inhibitors (69–73). While these preclinical data have not yet been translated into clinical success, this strategy remains appealing and more trials with the aim of restoring functional NIS expression and sensitivity to RAI are underway.

■ ANAPLASTIC THYROID CARCINOMA

Anaplastic thyroid carcinoma (ATC) constitutes approximately 2% of all thyroid cancers (51,74,75). While the incidence of ATC has been declining over the last few decades, it remains one of the most aggressive and lethal human cancers, with a nearly 100% disease-specific mortality and a median survival of 4 to 6 months (74,76,77). There are several reasons why the incidence of this cancer has been declining. Anaplastic thyroid carcinoma can arise de novo or result from the dedifferentiation of well-differentiated papillary and follicular thyroid carcinomas (74,78,79). Therefore, early detection and appropriate management of DTC should preclude the development of some ATCs. ATCs are also associated with goiter due to iodine

deficiency. Hence goiter prevention with iodized salt may also be responsible for the declining incidence of ATC (74,80). Lastly, more precise histologic classification of some thyroid cancer variants, such as insular carcinoma, poorly differentiated thyroid carcinoma, and undifferentiated medullary thyroid carcinoma, is thought to have contributed to a decrease in the diagnosis of ATC (79).

ATC most commonly presents in the seventh decade of life, and occurs more in women than men (74,79). The initial presentation of ATC typically involves a rapidly enlarging neck mass that can compress and/or invade surrounding structures in the neck, such as the esophagus, recurrent laryngeal nerve, and trachea, leading to dysphagia, hoarseness, dyspnea, and stridor. Lymph nodes metastases are frequent, and distant metastases are seen in approximately half of patients at diagnosis (74,76,80). By AJCC TNM classification, all ATCs are stage IV, with stage IVA representing resectable disease, IVB representing unresectable disease without distant metastasis, and IVC ATC with distant metastasis (10).

The diagnosis of anaplastic thyroid carcinoma is suspected when a patient presents with rapidly growing neck mass. The histology of ATC is pleomorphic with bizarre, irregular cells. FNA is diagnostic of ATC in approximately 90% of cases; however, tumor necrosis, hemorrhage, areas of coexisting DTC, and phenotypic variants that share features with other tumor types, such as giant osteoclast-like, spindle, or squamoid morphology, can make diagnosis by FNA alone problematic. Because of the clinical implications of misclassifying ATC, a more definitive tissue biopsy is indicated to confirm a diagnosis of ATC and rule out other diagnoses including lymphoma, medullary thyroid carcinoma, and the insular variant of follicular thyroid carcinoma (74,81,82).

ATCs typically harbor multiple genetic abnormalities (77,83). In addition to frequent chromosomal gains and losses, gene amplifications and deletions, mutations in a number of genes are seen. Mutations in *RAS* and *BRAF* that are characteristic of DTCs are also seen frequently in ATC,

suggesting that these mutations are early events in carcinogenesis (21,84). Late mutations can involve p53, β -catenin, and PIK3CA and are thought to represent seminal events in the dedifferentiation of DTC into ATC (78,79,85–89).

The management of ATC is particularly challenging because most patients with ATC present with both extensive locoregional disease and distant metastasis. The rarity of ATC makes it difficult to conduct prospective clinical trials, and therefore most data are derived from single institution reports. Several series have reported better outcomes in patients with completely resected neck disease, and long-term survival has essentially been reported only in patients who have undergone complete resection, often in the setting of incidentally discovered disease (80,90–93). While patients with intrathyroidal disease are the best candidates for surgery, those with limited extrathyroidal extension may also benefit from surgical resection (76,93). Adjuvant chemoradiotherapy is generally considered essential to improve locoregional control and prevent death from airway obstruction. IMRT may allow for the delivery of higher dose to the thyroid bed and regional nodes, with better sparing of normal tissues than three-dimensional radiotherapy (94). Hyperfractionated radiotherapy with or without concurrent doxorubicin-based chemotherapy has also been studied to enhance locoregional control. While most patients in these studies did not succumb to locoregional disease, treatment-related toxicity was problematic, most patients developed distant metastasis, and median survival ranged from only 3 to 10 months (93,95–97). Doxorubicin is the agent most utilized for radiation sensitization, though no study has demonstrated a survival benefit from the addition of chemotherapy to radiation (95). Thus, even for the minority of ATC patients who are able to undergo resection and adjuvant chemoradiotherapy, a significant unmet need for more effective therapy remains.

In addition to doxorubicin, other cytotoxic chemotherapies that have been examined in ATC include paclitaxel and docetaxel monotherapy and combination regimens such as doxorubicin plus

cisplatin, and cisplatin, bleomycin, and doxorubicin (56,98–100). While combination chemotherapy may yield higher response rates, as seen in the randomized Eastern Cooperative Group study investigating doxorubicin with or without cisplatin, there is no clear survival benefit that would justify the greater toxicity of combination therapy (56).

New therapies for ATC are emerging. The vascular disrupting agent, fosbretabulin, showed preclinical and phase I activity against ATC and was studied in a phase II study enrolling 28 patients (101). While there were no objective responses, several patients experienced stable disease with a median duration of 12 months. A subsequent clinical trial investigating fosbretabulin in combination with carboplatin/paclitaxel chemotherapy is underway. Other attempts to improve outcomes in ATC by targeting angiogenesis include investigations of VEGFR TKIs and the VEGF monoclonal antibody bevacizumab. A phase II trial of axitinib included two patients with ATC, one of whom had a partial response (61). Responses to sorafenib have also been reported, leading to a multicenter phase II study that is currently enrolling patients (102). Similarly, sunitinib is being studied in a French multicenter phase II study (65). Lastly, bevacizumab is being studied in Sweden in the curative setting, added to hyperfractionated radiation, doxorubicin, and surgery.

Other targets of interest in ATC include platelet-derived growth factor receptor, shown to be overexpressed in gene expression array, leading to a phase II study of imatinib. Two of 11 patients enrolled in this study had a partial response. Peroxisome proliferator-activated receptor gamma (PPARG), a transcription factor involved in follicular cell differentiation, can also be targeted with therapeutic intent by PPARG agonists, which have shown in vitro antitumor activity in several cancer types. The PPARG agonist, CS7017, has recently been explored in a phase I/II study in combination with paclitaxel for patients with ATC. Other potential molecular targets that may be promising include ras/RAF/MEK and PI-3K/AKT/mTOR pathways, as well as combined inhibition of these pathways (68). The clinical development of targeted therapy for ATC is

made especially difficult by the rarity of the disease and the aggressiveness of the clinical presentation.

■ MEDULLARY THYROID CARCINOMA

MTC is a tumor that arises from calcitonin-producing parafollicular C cells in the thyroid. MTC is sporadic in 75% to 80% of cases and hereditary in 20% to 25% of cases, where it is associated with germline mutations in the RET oncogene, and Multiple Endocrine Neoplasia type 2 (MEN2) (103,104). The identification of individuals with hereditary MTC is critically important since family members also affected by the germline mutation must be identified, and patients are at risk for other endocrine cancers, including pheochromocytoma and parathyroid hyperplasia. Strong associations between particular RET genotypes and the penetrance of other MEN2 neoplasms exist. Patients with hereditary MTC and MEN2 should be referred for genetic counseling. All patients with newly diagnosed MTC should undergo genetic testing to establish whether they have sporadic or hereditary disease (105–107).

The germline mutation in the RET protooncogene present in hereditary forms of MTC is inherited in an autosomal dominant fashion (106). Individuals with sporadic MTC harbor somatic mutations in RET, which can be identified in approximately 45% of individual tumors (108–111). RET resides on chromosome 10 and encodes a transmembrane tyrosine kinase receptor that is highly expressed in cells that are neural crest derivatives, such as the thyroid C cells, adrenal medullary cells, and the neurons of the kidney and gut. Activation of RET by its ligands, such as glial cell derived-neurotrophic factor, leads to receptor homodimerization and autophosphorylation of the intracellular tyrosine kinase domain, which further activates pathways involved in cell survival, proliferation, and differentiation, such as the Ras/ERK, PI-3K/AKT, and β -catenin/WNT pathways.

Mutations in RET are generally single amino acid changes that activate the receptor (108,112).

Individuals with germline RET mutations are at risk for pheochromocytoma. The risk varies by the mutation in RET, and family history is often a reliable guide for the penetrance within a particular kindred. These individuals need to undergo biochemical and/or imaging to screen for pheochromocytoma (106,107).

The presentation of MTC is variable and may range from an isolated thyroid nodule to metastatic disease at presentation. Serum calcitonin is generally elevated and the magnitude of elevation is a rough indication of the total volume of disease. High calcitonin levels can be associated with diarrhea and flushing, whereas patients with synchronous pheochromocytoma may complain of headache and diaphoresis (106,108,113). The initial test most frequently used to diagnose MTC is a FNA of a thyroid nodule and subsequent measurement of serum calcitonin, if MTC is suspected (114,115). Genetic testing should be performed to exclude a germline mutation and MEN 2. Biochemical screening to exclude pheochromocytoma is generally performed preoperatively (105,108).

Surgery plays a central role in the management of MTC. Preoperative neck ultrasound is recommended for all patients when an FNA and/or calcitonin level is suspicious for MTC, particularly because cervical nodal metastasis is common at presentation (116). Preoperative neck and chest CT, and liver CT or MRI is also generally recommended for suspected MTC patients if there is evidence of cervical nodal metastasis or the serum calcitonin is >400 pg/ml (117). A total thyroidectomy is recommended for all patients with newly diagnosed MTC. Bilateral prophylactic level VI central lymph node dissection is generally performed for patients with MTC regardless of clinical or radiographic evidence of nodal metastasis, due to a high rate of occult lymph node metastasis in these patients. At present, surgical management of the lateral compartment of the neck is variable, with some surgeons preferring to dissect levels IIA, III, IV, and V only when there is radiographic evidence of involvement. That said,

the goal of surgery is to perform complete resection at the initial procedure, as the risk of complications increases with reoperation (105,108,118).

The TNM staging system is the most frequently used staging system for MTC; however, it does not take into account other several prognostic factors, such as postoperative calcitonin level or postoperative calcitonin and CEA doubling times, which are predictive of overall survival (10,119). Postoperative surveillance with calcitonin and CEA levels are recommended to detect persistent or recurrent disease. Levels are usually measured 2 to 4 months following surgery because of a long half-life and inflammatory effects on calcitonin synthesis, and elevated levels may indicate local disease or distant metastasis, warranting further evaluation. For example, calcitonin of up to 150 pg/ml may suggest persistent neck disease and neck ultrasound at a minimum should be considered. In patients with calcitonin >150 pg/ml, distant metastasis is more likely, and imaging of the neck, chest, abdomen, and bones is recommended. Negative imaging of the neck and chest with high calcitonin levels may indicate the presence of liver metastasis, in which case 3-phase contrast-enhanced liver CT or contrast-enhanced MRI may be performed, as metastatic MTC often presents with subtle liver infiltration (105,106).

MTC is not highly responsive cytotoxic chemotherapy and EBRT, underscoring the importance of surgical resection as the primary treatment modality for the disease. However, radiotherapy is considered in the adjuvant setting or for palliative treatment for extensive neck or mediastinal disease. While prospective controlled studies have not been performed, several recent single-institution retrospective reviews indicate that postoperative EBRT can contribute to locoregional control of MTC, particularly in high-risk patients with multiple involved lymph nodes, nodal extracapsular extension, extrathyroidal extension, positive margins, and gross residual/unresectable disease (49,113,120).

Historically, cytotoxic chemotherapy was used in metastatic or locally recurrent unresectable MTC, though there is little evidence to support its use.

Activity of doxorubicin, doxorubicin plus cisplatin, and dacarbazine-based therapy in MTC has been reported; however, the data are difficult to interpret because the response rates are low, sample sizes are small, response criteria are variable, and MTC, even when advanced, has a variable clinical course with median survival ranging from 2 to 4 years, making comparison between studies difficult (121–123).

Recent studies indicate activity for several drugs with anti-RET activity in patients with metastatic MTC (61,66,124–131). Vandetanib, sorafenib, sunitinib, motesanib, and XL184 have shown the most early promise. Based upon preclinical inhibitory activity against RET, as well as VEGF and EGFR, vandetanib was studied in hereditary MTC (132). Thirty patients with advanced hereditary MTC were treated with vandetanib in a phase II multicenter study (124). The rate of partial response by RECIST (Response Evaluation Criteria In Solid Tumors) was 20%, with an additional 53% of patients experiencing stable disease for at least 24 weeks, and median PFS of 30 months. These results led to an international placebo-controlled phase III study in 331 patients with sporadic or hereditary advanced MTC that has now been reported in abstract form (125). The primary endpoint was PFS, and a statistically significant improvement with vandetanib was found, 19.8 months with placebo versus PFS not reached with vandetanib (hazard ratio = 0.45). The side-effect profile included frequent GI toxicity, hypertension, and headache, with toxicities leading to dose reduction in 35% of patients. However, with a median follow-up of 24 months, almost half of patients remained on blinded treatment, indicating durable tolerability despite the adverse effects.

Motesanib is a similar VEGFR TKI studied in the phase II setting. Ninety-one MTC patients were enrolled, and while there were few objective responses seen, 81% of patients had stable disease (128). Of note, pharmacokinetic studies showed lower serum drug concentrations in MTC patients compared to those measured in DTC patients enrolled on a parallel motesanib study, and this may

have muted the drug's activity. Reports of small numbers of MTC patients responding to other VEGFR TKIs, such as sorafenib, sunitinib, axitinib, and XL184 confirm that this class of agents has clear activity in MTC (64–66,126,129–131,133). Of these, XL184, an oral inhibitor of VEGFR2 and C-MET in addition to RET, showed particular promise in a phase I study enriched for patients with MTC (131,133). As a result, a randomized placebo-controlled study investigating XL184 in MTC patients with a target accrual of 315 patients is underway.

Thinking beyond RET as a target in MTC is also of interest. Firstly, responses to VEGFR TKIs have been seen in patients with sporadic MTC whose tumor does not harbor a RET mutation, indicating RET-independent mechanisms of response (131). In addition, other receptor tyrosine kinases, such as epidermal growth factor receptor and fibroblast growth factor receptor, other signal transduction pathways, such as the PI-3K/AKT/mTOR pathway, and tumor suppressor genes, such as P18 and p53, may be involved in the pathogenesis of MTC (78). As our understanding of the interaction of the various molecular pathways involved in MTC matures, and more targeted therapies become available, new agents as well as combinatorial approaches are certain to be explored in order to continue building upon the most recent steps forward.

■ SUMMARY

The preceding decade has brought about major progress in the treatment of thyroid cancer, particularly for patients with complex disease. Surgery remains the mainstay of therapy, but is complemented by radioiodine and/or radiotherapy in many cases. And now there is an emerging role for medical oncology, particularly in the management of advanced, iodine-refractory thyroid cancer. The optimal management is often best provided by a team approach that can involve surgery, endocrinology, nuclear medicine, and even radiation

and medical oncology. Coordinated, integrated care plus further progress in new treatment options should continue to lead to exciting developments in the field and improved outcomes for our patients.

REFERENCES

1. National Cancer Institute. SEER Cancer Statistics Review, 1975–2007. 2010. http://seer.cancer.gov/csr/1975_2007/. Accessed.
2. Enewold L, Zhu K, Ron E, et al. Rising thyroid cancer incidence in the United States by demographic and tumor characteristics, 1980–2005. *Cancer Epidemiol Biomarkers Prev*. 2009;18(3):784–791.
3. Chen AY, Jemal A, Ward EM. Increasing incidence of differentiated thyroid cancer in the United States, 1988–2005. *Cancer*. 2009;115(16):3801–3807.
4. Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973–2002. *JAMA*. 2006;295(18):2164–2167.
5. Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. *Am J Med*. 1994;97(5):418–428.
6. Hundahl SA, Fleming ID, Fremgen AM, Menck HR. A National Cancer Data Base report on 53,856 cases of thyroid carcinoma treated in the U.S., 1985–1995 [see comments]. *Cancer*. 1998;83(12):2638–2648.
7. DeLellis RA, Lloyd RV, Heitz PU, Eng C. *Pathology and Genetics of Endocrine Tumors*. Lyon: IARC Press; 2004.
8. Shattuck TM, Westra WH, Ladenson PW, Arnold A. Independent clonal origins of distinct tumor foci in multifocal papillary thyroid carcinoma. *N Engl J Med*. 2005;352(23):2406–2412.
9. Giannini R, Ugolini C, Lupi C, et al. The heterogeneous distribution of BRAF mutation supports the independent clonal origin of distinct tumor foci in multifocal papillary thyroid carcinoma. *J Clin Endocrinol Metab*. 2007;92(9):3511–3516.
10. Edge SB, Byrd DR, Compton CC, Fritz AG, Green FL, Trotti Ae. *AJCC Cancer Staging Manual*. New York, NY: Springer; 2010.
11. Hay ID, Bergstralh EJ, Goellner JR, Ebersold JR, Grant CS. Predicting outcome in papillary thyroid carcinoma: development of a reliable prognostic scoring system in a cohort of 1779 patients surgically treated at one institution during 1940 through 1989. *Surgery*. 1993;114(6):1050–1057; discussion 7–8.
12. Toniato A, Boschin I, Casara D, Mazzarotto R, Rubello D, Pelizzo M. Papillary thyroid carcinoma: factors influencing recurrence and survival. *Ann Surg Oncol*. 2008;15(5):1518–1522.
13. Falvo L, Giacomelli L, D'Andrea V, Marzullo A, Guerriero G, de Antoni E. Prognostic importance of sclerosing variant in papillary thyroid carcinoma. *Am Surg*. 2006;72(5):438–444.
14. Agha A, Glockzin G, Woencckhaus M, Dietmaier W, Iesalnieks I, Schlitt HJ. Insular carcinomas of the thyroid exhibit poor prognosis and long-term survival in comparison to follicular and papillary T4 carcinomas. *Langenbecks Arch Surg*. 2007;392(6):671–677.
15. Gosssein RA, Hiltzik DH, Carlson DL, et al. Prognostic factors of recurrence in encapsulated Hurthle cell carcinoma of the thyroid gland: a clinicopathologic study of 50 cases. *Cancer*. 2006;106(8):1669–1676.
16. Robbins RJ, Wan Q, Grewal RK, et al. Real-time prognosis for metastatic thyroid carcinoma based on 2-[18F]fluoro-2-deoxy-D-glucose-positron emission tomography scanning. *J Clin Endocrinol Metab*. 2006; 91(2):498–505.
17. Sciuto R, Romano L, Rea S, Marandino F, Sperduti I, Maini CL. Natural history and clinical outcome of differentiated thyroid carcinoma: a retrospective analysis of 1503 patients treated at a single institution. *Ann Oncol*. 2009;20(10):1728–1735.
18. Xing M, Westra WH, Tufano RP, et al. BRAF mutation predicts a poorer clinical prognosis for papillary thyroid cancer. *J Clin Endocrinol Metab*. 2005; 90(12):6373–6379.
19. Nikiforova MN, Kimura ET, Gandhi M, et al. BRAF mutations in thyroid tumors are restricted to papillary carcinomas and anaplastic or poorly differentiated carcinomas arising from papillary carcinomas. *J Clin Endocrinol Metab*. 2003;88(11):5399–5404.
20. Kebebew E, Weng J, Bauer J, et al. The prevalence and prognostic value of BRAF mutation in thyroid cancer. *Ann Surg*. 2007;246(3):466–470; discussion 470–471.
21. Ricarte-Filho JC, Ryder M, Chitale DA, et al. Mutational profile of advanced primary and metastatic radioactive iodine-refractory thyroid cancers reveals distinct pathogenetic roles for BRAF, PIK3CA, and AKT1. *Cancer Res*. 2009;69(11):4885–4893.
22. Lewis TS, Shapiro PS, Ahn NG. Signal transduction through MAP kinase cascades. *Adv Cancer Res*. 1998; 74:49–139.
23. Cohen Y, Xing M, Mambo E, et al. BRAF mutation in papillary thyroid carcinoma. *J Natl Cancer Inst*. 2003;95(8):625–627.
24. Fukushima T, Suzuki S, Mashiko M, et al. BRAF mutations in papillary carcinomas of the thyroid. *Oncogene*. 2003;22(41):6455–6457.

25. Kimura ET, Nikiforova MN, Zhu Z, Knauf JA, Nikiforov YE, Fagin JA. High prevalence of BRAF mutations in thyroid cancer: genetic evidence for constitutive activation of the RET/PTC-RAS-BRAF signaling pathway in papillary thyroid carcinoma. *Cancer Res.* 2003;63(7):1454–1457.
26. Soares P, Trovisco V, Rocha AS, et al. BRAF mutations and RET/PTC rearrangements are alternative events in the etiopathogenesis of PTC. *Oncogene.* 2003;22(29):4578–4580.
27. Xu X, Quiros RM, Gattuso P, Ain KB, Prinz RA. High prevalence of BRAF gene mutation in papillary thyroid carcinomas and thyroid tumor cell lines. *Cancer Res.* 2003;63(15):4561–4567.
28. Namba H, Nakashima M, Hayashi T, et al. Clinical implication of hot spot BRAF mutation, V599E, in papillary thyroid cancers. *J Clin Endocrinol Metab.* 2003;88(9):4393–4397.
29. DeLellis RA. Pathology and genetics of thyroid carcinoma. *J Surg Oncol.* 2006;94(8):662–669.
30. Nikiforov YE. RET/PTC rearrangement in thyroid tumors. *Endocr Pathol.* 2002;13(1):3–16.
31. Nikiforov YE, Rowland JM, Bove KE, Monforte-Munoz H, Fagin JA. Distinct pattern of ret oncogene rearrangements in morphological variants of radiation-induced and sporadic thyroid papillary carcinomas in children. *Cancer Res.* 1997;57(9):1690–1694.
32. Fugazzola L, Pilotti S, Pinchera A, et al. Oncogenic rearrangements of the RET proto-oncogene in papillary thyroid carcinomas from children exposed to the Chernobyl nuclear accident. *Cancer Res.* 1995;55(23):5617–5620.
33. Klugbauer S, Lengfelder E, Demidchik EP, Rabes HM. High prevalence of RET rearrangement in thyroid tumors of children from Belarus after the Chernobyl reactor accident. *Oncogene.* 1995;11(12):2459–2467.
34. Smida J, Salassidis K, Hieber L, et al. Distinct frequency of ret rearrangements in papillary thyroid carcinomas of children and adults from Belarus. *Int J Cancer.* 1999;80(1):32–38.
35. Rabes HM, Demidchik EP, Sidorow JD, et al. Pattern of radiation-induced RET and NTRK1 rearrangements in 191 post-chernobyl papillary thyroid carcinomas: biological, phenotypic, and clinical implications. *Clin Cancer Res.* 2000;6(3):1093–1103.
36. Santoro M, Carlomagno F, Hay ID, et al. Ret oncogene activation in human thyroid neoplasms is restricted to the papillary cancer subtype. *J Clin Invest.* 1992;89(5):1517–1522.
37. Jhiang SM, Caruso DR, Gilmore E, et al. Detection of the PTC/retTPC oncogene in human thyroid cancers. *Oncogene.* 1992;7(7):1331–1337.
38. Nikiforova MN, Caudill CM, Biddinger P, Nikiforov YE. Prevalence of RET/PTC rearrangements in Hashimoto's thyroiditis and papillary thyroid carcinomas. *Int J Surg Pathol.* 2002;10(1):15–22.
39. Lam AK, Montone KT, Nolan KA, Livolsi VA. Ret oncogene activation in papillary thyroid carcinoma: prevalence and implication on the histological parameters. *Hum Pathol.* 1998;29(6):565–568.
40. Di Cristofaro J, Marcy M, Vasko V, et al. Molecular genetic study comparing follicular variant versus classic papillary thyroid carcinomas: association of N-ras mutation in codon 61 with follicular variant. *Hum Pathol.* 2006;37(7):824–830.
41. Kondo T, Ezzat S, Asa SL. Pathogenetic mechanisms in thyroid follicular-cell neoplasia. *Nat Rev Cancer.* 2006;6(4):292–306.
42. Nikiforova MN, Lynch RA, Biddinger PW, et al. RAS point mutations and PAX8-PPAR gamma rearrangement in thyroid tumors: evidence for distinct molecular pathways in thyroid follicular carcinoma. *J Clin Endocrinol Metab.* 2003;88(5):2318–2326.
43. Cooper DS, Doherty GM, Haugen BR, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid.* 2009;19(11):1167–1214.
44. Sherman SI. Thyroid carcinoma. *Lancet.* 2003;361(9356):501–511.
45. Hay ID, Thompson GB, Grant CS, et al. Papillary thyroid carcinoma managed at the Mayo Clinic during six decades (1940–1999): temporal trends in initial therapy and long-term outcome in 2444 consecutively treated patients. *World J Surg.* 2002;26(8):879–885.
46. Bilimoria KY, Bentrem DJ, Ko CY, et al. Extent of surgery affects survival for papillary thyroid cancer. *Ann Surg.* 2007;246(3):375–381; discussion 381–384.
47. Pinchot SN, Sippel RS, Chen H. Multi-targeted approach in the treatment of thyroid cancer. *Ther Clin Risk Manag.* 2008;4(5):935–947.
48. Sosa JA, Bowman HM, Tielsch JM, Powe NR, Gordon TA, Udelsman R. The importance of surgeon experience for clinical and economic outcomes from thyroidectomy. *Ann Surg.* 1998;228(3):320–330.
49. Terezakis SA, Lee KS, Ghossein RA, et al. Role of external beam radiotherapy in patients with advanced or recurrent nonanaplastic thyroid cancer: Memorial Sloan-Kettering Cancer Center experience. *Int J Radiat Oncol Biol Phys.* 2009;73(3):795–801.
50. Schwartz DL, Lobo MJ, Ang KK, et al. Postoperative external beam radiotherapy for differentiated thyroid cancer: outcomes and morbidity with conformal treatment. *Int J Radiat Oncol Biol Phys.* 2009;74(4):1083–1091.

51. Gilliland FD, Hunt WC, Morris DM, Key CR. Prognostic factors for thyroid carcinoma. A population-based study of 15,698 cases from the Surveillance, Epidemiology and End Results (SEER) program 1973–1991. *Cancer*. 1997;79(3):564–573.
52. Durante C, Haddy N, Baudin E, et al. Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: benefits and limits of radioiodine therapy. *J Clin Endocrinol Metab*. 2006;91(8):2892–2899.
53. Tuttle RM. Risk-adapted management of thyroid cancer. *Endocr Pract*. 2008;14(6):764–774.
54. Gottlieb JA, Hill CS, Jr. Chemotherapy of thyroid cancer with adriamycin. Experience with 30 patients. *N Engl J Med*. 1974;290(4):193–197.
55. Matuszczyk A, Petersenn S, Bockisch A, et al. Chemotherapy with doxorubicin in progressive medullary and thyroid carcinoma of the follicular epithelium. *Horm Metab Res*. 2008;40(3):210–213.
56. Shimaoka K, Schoenfeld DA, DeWys WD, Creech RH, DeConti R. A randomized trial of doxorubicin versus doxorubicin plus cisplatin in patients with advanced thyroid carcinoma. *Cancer*. 1985;56(9):2155–2160.
57. Williams SD, Birch R, Einhorn LH. Phase II evaluation of doxorubicin plus cisplatin in advanced thyroid cancer: a Southeastern Cancer Study Group Trial. *Cancer Treat Rep*. 1986;70(3):405–407.
58. Bukowski RM, Brown L, Weick JK, Groppe CW, Purvis J. Combination chemotherapy of metastatic thyroid cancer. Phase II study. *Am J Clin Oncol*. 1983;6(5):579–581.
59. Droz JP, Schlumberger M, Rougier P, Ghosn M, Gardet P, Parmentier C. Chemotherapy in metastatic nonanaplastic thyroid cancer: experience at the Institut Gustave-Roussy. *Tumori*. 1990;76(5):480–483.
60. Sherman SI, Wirth LJ, Droz JP, et al. Motesanib diphosphate in progressive differentiated thyroid cancer. *N Engl J Med*. 2008;359(1):31–42.
61. Cohen EE, Rosen LS, Vokes EE, et al. Axitinib is an active treatment for all histologic subtypes of advanced thyroid cancer: results from a phase II study. *J Clin Oncol*. 2008;26(29):4708–4713.
62. Kloos RT, Ringel MD, Knopp MV, et al. Phase II trial of sorafenib in metastatic thyroid cancer. *J Clin Oncol*. 2009;27(10):1675–1684.
63. Gupta-Abramson V, Troxel AB, Nellore A, et al. Phase II trial of sorafenib in advanced thyroid cancer. *J Clin Oncol*. 2008;26(29):4714–4719.
64. Cohen EE, Needles BM, Cullen KJ, et al. Phase 2 study of sunitinib in refractory thyroid cancer [Abstract 6025]. *J Clin Oncol*. 2008;26(suppl).
65. Ravaud A, de la Fouchardière C, Courbon F, et al. Sunitinib in patients with refractory advanced thyroid cancer: the THYSU phase II trial [Abstract 6058]. *J Clin Oncol*. 2008;26(suppl).
66. Carr L, Goulart B, Martins R, et al. Phase II trial of continuous dosing of sunitinib in advanced, FDG-PET avid, medullary thyroid carcinoma (MTC) and well-differentiated thyroid cancer (WDTC) [Abstract 6056]. *J Clin Oncol*. 2009;27(15s)(suppl).
67. Bible KC, Smallridge RC, Maples WJ, et al. Phase II trial of Pazopanib in progressive, metastatic, iodine-insensitive differentiated thyroid cancers. [Abstract 3521]. *J Clin Oncol*. 2009;27(15s)(suppl).
68. Jin N, Jiang T, Rosen DM, Nelkin BD, Ball DW. Dual inhibition of mitogen-activated protein kinase kinase and mammalian target of rapamycin in differentiated and anaplastic thyroid cancer. *J Clin Endocrinol Metab*. 2009;94(10):4107–4112.
69. Schmutzler C, Brtko J, Bienert K, Kohrle J. Effects of retinoids and role of retinoic acid receptors in human thyroid carcinomas and cell lines derived therefrom. *Exp Clin Endocrinol Diabetes*. 1996;104(suppl 4):16–19.
70. Martelli ML, Iuliano R, Le Pera I, et al. Inhibitory effects of peroxisome proliferator-activated receptor gamma on thyroid carcinoma cell growth. *J Clin Endocrinol Metab*. 2002;87(10):4728–4735.
71. Kebebew E, Peng M, Reiff E, et al. A phase II trial of rosiglitazone in patients with thyroglobulin-positive and radioiodine-negative differentiated thyroid cancer. *Surgery*. 2006;140(6):960–966; discussion 6–7.
72. Tepmongkol S, Keelawat S, Honsawek S, Ruangvejvorachai P. Rosiglitazone effect on radioiodine uptake in thyroid carcinoma patients with high thyroglobulin but negative total body scan: a correlation with the expression of peroxisome proliferator-activated receptor-gamma. *Thyroid*. 2008;18(7):697–704.
73. Kitazono M, Robey R, Zhan Z, et al. Low concentrations of the histone deacetylase inhibitor, depsipeptide (FR901228), increase expression of the Na(+)/I(−) symporter and iodine accumulation in poorly differentiated thyroid carcinoma cells. *J Clin Endocrinol Metab*. 2001;86(7):3430–3435.
74. Are C, Shaha AR. Anaplastic thyroid carcinoma: biology, pathogenesis, prognostic factors, and treatment approaches. *Ann Surg Oncol*. 2006;13(4):453–464.
75. Landis SH, Murray T, Bolden S, Wingo PA. Cancer statistics, 1998. *CA Cancer J Clin*. 1998;48(1):6–29.
76. Kebebew E, Greenspan FS, Clark OH, Woerber KA, McMillan A. Anaplastic thyroid carcinoma. Treatment outcome and prognostic factors. *Cancer* 2005;103(7):1330–1335.

77. Smallridge RC, Copland JA. Anaplastic thyroid carcinoma: pathogenesis and emerging therapies. *Clin Oncol (R Coll Radiol)*. 2010;22(6):486–97.
78. Santarpia L, El-Naggar AK, Cote GJ, Myers JN, Sherman SI. Phosphatidylinositol 3-kinase/akt and ras/raf-mitogen-activated protein kinase pathway mutations in anaplastic thyroid cancer. *J Clin Endocrinol Metab*. 2008;93(1):278–284.
79. Neff RL, Farrar WB, Kloos RT, Burman KD. Anaplastic thyroid cancer. *Endocrinol Metab Clin North Am*. 2008;37(2):525–538; xi.
80. Passler C, Scheuba C, Prager G, et al. Anaplastic (undifferentiated) thyroid carcinoma (ATC). A retrospective analysis. *Langenbecks Arch Surg*. 1999;384(3):284–293.
81. Cleary JM, Sadow PM, Randolph GW, et al. Neoadjuvant treatment of unresectable medullary thyroid cancer with sunitinib. *J Clin Oncol*. 2010;28(23):e390–e392.
82. Carcangiu ML, Steeper T, Zampi G, Rosai J. Anaplastic thyroid carcinoma. A study of 70 cases. *Am J Clin Pathol*. 1985;83(2):135–158.
83. Smallridge RC, Marlow LA, Copland JA. Anaplastic thyroid cancer: molecular pathogenesis and emerging therapies. *Endocrine-related cancer*. 2009;16(1):17–44.
84. Nikiforov YE. Genetic alterations involved in the transition from well-differentiated to poorly differentiated and anaplastic thyroid carcinomas. *Endocr Pathol*. 2004;15(4):319–327.
85. Wiseman SM, Masoudi H, Niblock P, et al. Anaplastic thyroid carcinoma: expression profile of targets for therapy offers new insights for disease treatment. *Ann Surg Oncol*. 2007;14(2):719–729.
86. Fagin JA, Matsuo K, Karmakar A, Chen DL, Tang SH, Koeffler HP. High prevalence of mutations of the p53 gene in poorly differentiated human thyroid carcinomas. *J Clin Invest*. 1993;91(1):179–184.
87. Garcia-Rostan G, Costa AM, Pereira-Castro I, et al. Mutation of the PIK3CA gene in anaplastic thyroid cancer. *Cancer Res*. 2005;65(22):10199–10207.
88. Wiseman SM, Griffith OL, Deen S, et al. Identification of molecular markers altered during transformation of differentiated into anaplastic thyroid carcinoma. *Arch Surg*. 2007;142(8):717–727; discussion 27–29.
89. Garcia-Rostan G, Tallini G, Herrero A, D'Aquila TG, Carcangiu ML, Rimm DL. Frequent mutation and nuclear localization of beta-catenin in anaplastic thyroid carcinoma. *Cancer Res*. 1999;59(8):1811–1815.
90. McIver B, Hay ID, Giuffrida DF, et al. Anaplastic thyroid carcinoma: a 50-year experience at a single institution. *Surgery*. 2001;130(6):1028–1034.
91. Pierie JP, Muzikansky A, Gaz RD, Faquin WC, Ott MJ. The effect of surgery and radiotherapy on outcome of anaplastic thyroid carcinoma. *Ann Surg Oncol*. 2002;9(1):57–64.
92. Haigh PI, Ituarte PH, Wu HS, et al. Completely resected anaplastic thyroid carcinoma combined with adjuvant chemotherapy and irradiation is associated with prolonged survival. *Cancer*. 2001; 91(12):2335–2342.
93. Swaak-Kragten AT, de Wilt JH, Schmitz PI, Bontenbal M, Levendag PC. Multimodality treatment for anaplastic thyroid carcinoma—treatment outcome in 75 patients. *Radiother Oncol*. 2009; 92(1):100–104.
94. Nutting CM, Convery DJ, Cosgrove VP, et al. Improvements in target coverage and reduced spinal cord irradiation using intensity-modulated radiotherapy (IMRT) in patients with carcinoma of the thyroid gland. *Radiother Oncol*. 2001;60(2):173–180.
95. Tennvall J, Lundell G, Wahlberg P, et al. Anaplastic thyroid carcinoma: three protocols combining doxorubicin, hyperfractionated radiotherapy and surgery. *Br J Cancer*. 2002;86(12):1848–1853.
96. De Crevoisier R, Baudin E, Bachelot A, et al. Combined treatment of anaplastic thyroid carcinoma with surgery, chemotherapy, and hyperfractionated accelerated external radiotherapy. *Int J Radiat Oncol Biol Phys*. 2004;60(4):1137–1143.
97. Dandekar P, Harmer C, Barbachano Y, et al. Hyperfractionated Accelerated Radiotherapy (HART) for anaplastic thyroid carcinoma: toxicity and survival analysis. *Int J Radiat Oncol Biol Phys*. 2009; 74(2):518–521.
98. Ain KB, Egorin MJ, DeSimone PA. Treatment of anaplastic thyroid carcinoma with paclitaxel: phase 2 trial using ninety-six-hour infusion. Collaborative Anaplastic Thyroid Cancer Health Intervention Trials (CATCHIT) Group. *Thyroid*. 2000;10(7): 587–594.
99. Kawada K, Kitagawa K, Kamei S, et al. The feasibility study of docetaxel in patients with anaplastic thyroid cancer. *Jpn J Clin Oncol*. 40(6):596–599.
100. De Besi P, Busnardo B, Toso S, et al. Combined chemotherapy with bleomycin, adriamycin, and platinum in advanced thyroid cancer. *J Endocrinol Invest*. 1991;14(6):475–480.
101. Mooney CJ, Nagaiah G, Fu P, et al. A phase II trial of fosbretabulin in advanced anaplastic thyroid carcinoma and correlation of baseline serum-soluble intracellular adhesion molecule-1 with outcome. *Thyroid*. 2009; 19(3):233–240.
102. Nagaiah G, Fu P, Wasman JK, et al. Phase II trial of sorafenib (bay 43-9006) in patients with advanced

- anaplastic carcinoma of the thyroid (ATC) [Abstract 6058]. *J Clin Oncol*. 2009;27(15s).
103. Saad MF, Ordonez NG, Rashid RK, et al. Medullary carcinoma of the thyroid. A study of the clinical features and prognostic factors in 161 patients. *Medicine (Baltimore)*. 1984;63(6):319–342.
 104. Kebebew E, Ituarte PH, Siperstein AE, Duh QY, Clark OH. Medullary thyroid carcinoma: clinical characteristics, treatment, prognostic factors, and a comparison of staging systems. *Cancer*. 2000; 88(5):1139–1148.
 105. Kloos RT, Eng C, Evans DB, et al. Medullary thyroid cancer: management guidelines of the American Thyroid Association. *Thyroid*. 2009;19(6):565–612.
 106. Jimenez C, Hu MI, Gagel RF. Management of medullary thyroid carcinoma. *Endocrinol Metab Clin North Am*. 2008;37(2):481–496; x–xi.
 107. You YN, Lakhani V, Wells SA Jr, Moley JF. Medullary thyroid cancer. *Surg Oncol Clin N Am*. 2006;15(3):639–660.
 108. Fialkowski EA, Moley JF. Current approaches to medullary thyroid carcinoma, sporadic and familial. *J Surg Oncol*. 2006;94(8):737–747.
 109. Mulligan LM, Ponder BA. Genetic basis of endocrine disease: multiple endocrine neoplasia type 2. *J Clin Endocrinol Metab*. 1995;80(7):1989–1995.
 110. Eng C. RET proto-oncogene in the development of human cancer. *J Clin Oncol*. 1999;17(1):380–393.
 111. Marsh DJ, Learoyd DL, Andrew SD, et al. Somatic mutations in the RET proto-oncogene in sporadic medullary thyroid carcinoma. *Clin Endocrinol (Oxf)*. 1996;44(3):249–257.
 112. Wells SA Jr, Santoro M. Targeting the RET pathway in thyroid cancer. *Clin Cancer Res*. 2009;15(23): 7119–7123.
 113. Brierley J, Tsang R, Simpson WJ, Gospodarowicz M, Sutcliffe S, Panzarella T. Medullary thyroid cancer: analyses of survival and prognostic factors and the role of radiation therapy in local control. *Thyroid*. 1996;6(4):305–310.
 114. Chang TC, Wu SL, Hsiao YL. Medullary thyroid carcinoma: pitfalls in diagnosis by fine needle aspiration cytology and relationship of cytomorphology to RET proto-oncogene mutations. *Acta Cytol*. 2005; 49(5):477–482.
 115. Elisei R, Bottici V, Luchetti F, et al. Impact of routine measurement of serum calcitonin on the diagnosis and outcome of medullary thyroid cancer: experience in 10,864 patients with nodular thyroid disorders. *J Clin Endocrinol Metab*. 2004;89(1):163–168.
 116. Moley JF, DeBenedetti MK. Patterns of nodal metastases in palpable medullary thyroid carcinoma: recommendations for extent of node dissection. *Ann Surg*. 1999;229(6):880–887; discussion 7–8.
 117. Machens A, Schneyer U, Holzhausen HJ, Dralle H. Prospects of remission in medullary thyroid carcinoma according to basal calcitonin level. *J Clin Endocrinol Metab*. 2005;90(4):2029–2034.
 118. Pelizzo MR, Boschin IM, Bernante P, et al. Natural history, diagnosis, treatment and outcome of medullary thyroid cancer: 37 years experience on 157 patients. *Eur J Surg Oncol*. 2007;33(4):493–497.
 119. Barbet J, Campion L, Kraeber-Bodere F, Chatal JF. Prognostic impact of serum calcitonin and carcinoembryonic antigen doubling-times in patients with medullary thyroid carcinoma. *J Clin Endocrinol Metab*. 2005;90(11):6077–6084.
 120. Schwartz DL, Rana V, Shaw S, et al. Postoperative radiotherapy for advanced medullary thyroid cancer—local disease control in the modern era. *Head Neck*. 2008;30(7):883–888.
 121. Droz JP, Rougier P, Goddefroy V, Schlumberger M, Gardet P, Parmentier C. [Chemotherapy for medullary cancer of the thyroid. Phase II trials with adriamycin and cis-platinum administered as monochemotherapy.] *Bull Cancer*. 1984;71(3):195–199.
 122. Scherubl H, Raue F, Ziegler R. Combination chemotherapy of advanced medullary and differentiated thyroid cancer. Phase II study. *J Cancer Res Clin Oncol*. 1990;116(1):21–23.
 123. Schlumberger M, Abdelmoumene N, Delisle MJ, Couette JE. Treatment of advanced medullary thyroid cancer with an alternating combination of 5 FU-streptozocin and 5 FU-dacarbazine. The Groupe d'Etude des Tumeurs a Calcitonine (GETC). *Br J Cancer*. 1995;71(2):363–365.
 124. Wells SA Jr, Gosnell JE, Gagel RF, et al. Vandetanib for the treatment of patients with locally advanced or metastatic hereditary medullary thyroid cancer. *J Clin Oncol*. 2010;28(5):767–772.
 125. Wells SA, Robinson BG, Gagel RF, et al. Vandetanib (VAN) in locally advanced or metastatic medullary thyroid cancer (MTC): A randomized, double-blind phase III trial (ZETA) [Abstract 5503]. *J Clin Oncol*. 2010;28(15s)(suppl).
 126. Kober F, Hermann M, Handler A, Krotla G. Effect of sorafenib in symptomatic metastatic medullary thyroid cancer [Abstract 14065]. *Journal of Clinical Oncology*. 2007;25(18S)(suppl).

127. Pennell NA, Daniels GH, Haddad RI, et al. A phase II study of gefitinib in patients with advanced thyroid cancer. *Thyroid*. 2008;18(3):317–323.
128. Schlumberger MJ, Elisei R, Bastholt L, et al. Phase II study of safety and efficacy of motesanib in patients with progressive or symptomatic, advanced or metastatic medullary thyroid cancer. *J Clin Oncol*. 2009;27(23):3794–3801.
129. Lam ET, Ringel MD, Kloos RT, et al. Phase II clinical trial of sorafenib in metastatic medullary thyroid cancer. *J Clin Oncol*. 2010;28(14):2323–2330.
130. De Souza JA, Busaidy N, Zimrin A, et al. Phase II trial of sunitinib in medullary thyroid carcinoma (MTC) [Abstract 5504]. *J Clin Oncol*. 2010;28(15s):(suppl).
131. Kurzrock R, Cohen EE, Sherman SI, et al. Long-term results in a cohort of medullary thyroid cancer (MTC) patients (pts) in a phase I study of XL184 (BMS 907351), an oral inhibitor of MET, VEGFR2, and RET [Abstract 5502]. *J Clin Oncol*. 2010;28(15s)(suppl).
132. Carlomagno F, Vitagliano D, Guida T, et al. ZD6474, an orally available inhibitor of KDR tyrosine kinase activity, efficiently blocks oncogenic RET kinases. *Cancer Res*. 2002;62(24):7284–7290.
133. Salgia R, Sherman S, Hong DS, et al. A phase I study of XL184, a RET, VEGFR2, and MET kinase inhibitor, in patients (pts) with advanced malignancies, including pts with medullary thyroid cancer (MTC) [Abstract 3522]. *J Clin Oncol*. 2008;26:(suppl).

CHAPTER 9

Evaluation and Treatment of Dysphagia and Aspiration in Head and Neck Cancer

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■ INTRODUCTION

Dysphagia is a complex problem that can present before, during, or after cancer treatments. Many patients with head and neck malignancy experience some degree of dysphagia, and some even have significant dysphagia leading to aspiration (1,2). The site of disease strongly correlates with the likelihood of pretreatment dysphagia and posttreatment dysphagia (2). While cancer treatment can improve tumor-related dysphagia via reduction in tumor bulk, treatments such as surgery, radiation, or chemotherapy can also cause dysphagia. Iatrogenic dysphagia can result from treatment effects on cranial nerves (both sensory and motor) or structural alterations from removal of normal structures, surgical scarring, or radiation/chemotherapy-associated fibrosis in the oral and pharyngeal areas.

Normal Swallow Physiology

Swallowing is a complex and highly coordinated act involving the bilateral sequencing of more than 25 pairs of muscles controlled primarily by 5 cranial nerves: the trigeminal (V), facial (VII), glossopharyngeal (IX), vagus (X), and hypoglossal (XII) (3). Normal swallowing involves a series of three progressive phases: oral, pharyngeal, and esophageal (4).

The oral phase of swallowing consists of both voluntary control and reflexive components. Anatomically, it includes the lips, tongue, superior alveolus, maxilla, inferior alveolus, floor of the mouth, buccal mucosa, retromolar trigone, and hard palate. During this first phase, food is manipulated by the tongue and, depending on its texture, masticated into a cohesive bolus. Mastication requires the temporalis, masseter, and medial and lateral pterygoid muscles to open and close the mandible. The facial muscles (i.e., orbicularis and buccinator) are triggered to seal the lips and close off the lateral sulci. Following mastication, the tongue, by activation of the genioglossus muscle, is positioned in the oral cavity so that its tip is against the alveolar ridge, thereby containing the bolus anteriorly between the tongue dorsum and hard palate. The intrinsic muscles of the tongue, along with the palatoglossus, are then activated to help contain the bolus in place. The actions completing bolus manipulation, formation, and containment are modulated by sensory feedback from the size, texture, taste, and temperature of the food or liquid (5).

Once formed, the bolus is propelled from the anterior oral cavity to the oropharynx by sequential contraction of the tongue. At this time, the lip and buccal muscles continue to contract, but the velum elevates and the posterior aspect of the

tongue depresses. The perimeter of the tongue remains in contact with the maxillary alveolar ridge while the tongue blade initiates first a centripetal motion and then a centrifugal motion, thereby driving the bolus posteriorly toward the oropharynx. As the bolus arrives in the oropharynx, the pharyngeal swallow is triggered, marking the start of the pharyngeal phase.

Within the oral cavity, there are 3 pairs of salivary glands: the parotid, submandibular, and sublingual glands. In addition to these primary glands, there is glandular tissue beneath the mucosal surface of the oral cavity, which excretes saliva through tiny openings called salivary ducts. The saliva produced by the combination of the salivary glands and ancillary salivary ducts is critical for swallowing (6). Its purpose is threefold: to prevent tooth decay and infections of the oral mucosa; to keep the oral mucosa moist thereby reducing friction as the bolus is propelled through the oropharynx; and, during mastication of especially dry and sticky foods, to help form a manageable bolus that travels efficiently through the oral cavity.

The pharyngeal phase begins as soon as the bolus arrives at the level of the tonsils and continues until the bolus enters the upper esophagus. During this phase, the bolus is moved through the pharynx without regurgitation into the nasal cavity or any aspiration into the larynx. Respiration and phonation are temporarily inhibited. The swallow in this phase is the most complex with several rapid and nearly synchronous events occurring, including velopharyngeal closure, glossopalatal junction opening, laryngeal closure, lingual bolus propulsion, pharyngeal clearance, and upper esophageal opening (7). The pharyngeal swallow is triggered when the larynx elevates, the arytenoids move anteriorly and the pharyngeal constrictor muscles (e.g., medial and inferior) contract. The constrictor muscles are activated in a fixed top-down sequence, generating a propulsive contractile wave helping drive the bolus into the esophagus. The order of muscle contraction in the pharyngeal

phase is constant, but there is adjustment in the temporal relationship among these movements according to the size and consistency of the bolus being swallowed. Failure of one or more of these movements may be compensated with changes in head and neck postures (see “Therapy” section).

The esophageal phase involves transporting the bolus down through the upper esophageal sphincter (UES) and toward the lower esophageal sphincter (LES). The cricopharyngeus muscle, typically in active contraction, relaxes in coordination with contraction of the pharyngeal constrictor muscles above. At the same time, the UES is pulled forward by the anterior and superior movements of the larynx. In so doing, a suction force is created at the level of the UES, which serves to draw the bolus through the open UES and into the esophagus (8). The bolus then travels by waves of peristaltic contractions through the esophagus to the level of the LES. Esophageal peristalsis is mediated by both central and local control.

The oral, pharyngeal, and esophageal phases are therefore three distinct anatomical regions that effectively integrate serially through a complex neuronal network. The oral phase is under voluntary control and can be stopped at any time. The pharyngeal and esophageal phases, in contrast, are triggered involuntarily and, therefore, once initiated are irreversible motor events. Anatomically, the swallowing control mechanism, also referred to as the “swallowing center,” is bilaterally represented by connected halves located in the medulla (9). There is evidence for 2 levels of integration within the swallowing center (10). The first level is a dorsal sensory area involved in the organization of the entire swallowing sequence. At this level, the swallow is initiated via sensory input from the neurons within the nucleus of the solitary tract and neighboring reticular formation. The second level is a ventral motor area that serves primarily to execute the swallowing sequence via excitation of the neurons in the nucleus ambiguus. The sensory input and feedback are critical to shape and initiate the motor execution of all three phases.

Iatrogenic Causes of Dysphagia in Head and Neck Cancer Patients

Although surgery and radiation can be used to definitively treat head and neck malignancy, they have been associated with posttreatment dysphagia. Of the patients who undergo surgical treatment, dysphagia is most prominent in the acute phase, but as many as half of these patients continue to have dysphagia at 3 years (11). Swallowing impairment is most severe in surgical patients with large amounts of tongue base resected (12). Standard postsurgical airway management can compound the postoperative swallowing problem. For example, a tracheotomy tube can restrict laryngeal elevation during the swallow,

thereby leading to aspiration (13). Fortunately, the degree of swallowing impairment secondary to surgical resection can be offset by careful reconstruction that maximizes bulk, mobility, and sensation in especially the oral, pharyngeal, and laryngeal areas (14–17). Table 9.1 presents a summary of certain surgical ablations and their associated swallowing impairments.

Swallowing problems may also occur in head and neck cancer patients whose cancer is addressed with nonsurgical organ preservation treatments. Multimodality treatment has been associated with increased rates of both acute and late toxicity for dysphagia (18). In these patients, prolonged tube feeding and inability to tolerate oral feeding have

TABLE 9.1

Common swallowing disorders from various surgeries to treat head and neck cancer

Area of Resection	Most Probable Swallowing Impairment
Oral sphincter	Difficulty in maintaining oral seal, resulting in drool or inability to take foods from a cup or spoon.
Anterior floor of mouth	Tongue mobility may be hindered, thereby affecting bolus manipulation during mastication and/or oral to pharyngeal bolus propulsion. Hyoid mobility may be hindered, thereby affecting opening of the cricopharyngeal sphincter and/or triggering of the pharyngeal swallow.
Tongue	Anterior resections tend to affect oral bolus manipulation during mastication and/or oral to pharyngeal bolus propulsion. This difficulty is further exacerbated if the tongue cannot make contact with the palate. Base of tongue resections tend to affect pharyngeal bolus drive from the pharynx to the esophagus.
Mandible	Loss of sensation in the teeth and lip. Jaw swing and malocclusion.
Palate	Reduced opposition for the oral tongue hinders bolus manipulation during mastication and/or oral to pharyngeal bolus propulsion. Loss of palatal to glottal seal, thereby permitting premature spillage of oral contents into the oropharynx, and/or nasal aspiration especially with liquids.
Pharynx	Reduced (to absent) pharyngeal peristalsis, thereby hindering clearance of bolus from pharyngeal cavity to esophagus, and/or triggering of the pharyngeal swallow. Dehiscence of the pharyngeal musculature may result in diverticuli and reduced pharyngeal bolus transport into the esophagus.
Larynx	In partial resections, airway protection can be severely compromised. In total resections, bolus-driving pressures are altered, thereby hindering opening of the cricopharyngeal sphincter.

been estimated to affect 10% to 20% of patients following concurrent chemotherapy and radiation. This impairment rate is increased as treatment is intensified, as with altered fractionation radiotherapy or concurrent chemotherapy and radiation approaches (19–23). Other factors that further increase the risk for swallowing problems in these patients include smoking during and after radiotherapy, depression, and poor mental health (24–26).

Chemoradiotherapy typically affects the range, coordination, and strength of tongue movements during swallowing (2). Less frequent, but also common, are problems with airway protection, pharyngeal peristalsis, and trigger of the pharyngeal swallow. Dysphagia and aspiration can begin and significantly worsen even years after the completion of treatment (27,28). This long-term swallowing impairment is thought to be a result of submucosal treatment effects, such as fibrosis, as well as sensory and motor nerve injury (29).

Complicating the dysphagia is the associated problem of xerostomia in patients treated with radiotherapy. Xerostomia consists of both acute and late aspects, each differing in response to preventive strategies (30). Each major salivary gland and the minor salivary glands play different roles in baseline and stimulated salivary production. Treatment-related alteration in either can lead to xerostomia and speech- and eating-related difficulties (31,32). However, monitoring xerostomia itself is difficult as there are complex (and sometimes paradoxical) relationships between salivary flow and patient-reported symptoms (33). As such, determining the relative contribution of xerostomia to dysphagia remains a daunting task.

How to Prevent Dysphagia From Iatrogenic Causes

A number of surgical issues that can contribute to dysphagia have been identified. Specifically, maximizing preservation of the normal tissue involved in the swallowing process appears to be quite important. For instance, preservation of lingual and hypoglossal nerves appears critical to prevent

development of oral dysphagia following head and neck surgery (14). Similarly, careful preservation of tongue base and pharyngeal structures associated with bolus propulsion appears necessary to prevent oropharyngeal dysfunction (12). However, even posttracheotomy patients should be monitored carefully for dysphagia as inflatable cuffs have been shown to affect the type and duration of dysphagia leading to aspiration (13).

Prevention of dysphagia following radiotherapy remains a challenging area of research as it is confounded by interactions with xerostomia. For both dysphagia and xerostomia, the general concept is to reduce the radiation dose and quantity of exposed tissue associated with swallowing or production of saliva. Eisbruch et al proposed the pharyngeal constrictors as the relevant radiotherapy target most closely linked to the development of post-radiotherapy dysphagia (1). After careful analysis of intensity-modulated radiation therapy (IMRT) treatments in patients with formal swallowing function tests before and after treatment, the pharyngeal constrictors and the glottic and supraglottic larynx were identified as most correlated with the development of dysphagia (34,35). Recently, the QUANTEC (Quantitative Analysis of Normal Tissue Effects in the Clinic) group performed a systematic review of radiotherapy-related dysphagia, which suggested that mean doses of 50 to 60 Gy appear to be associated with a 50% risk of toxicity and, whenever possible, constrictors and other swallowing structures should have doses reduced to below this threshold (36) (see Table 9.2). A predictive model of dysphagia following radiation therapy that uses a nomogram-type approach including site of disease and other treatment factors has also been proposed (37) (see Figure 9.1).

How to Prevent Xerostomia From Iatrogenic Causes

The most logical way to prevent xerostomia following radiotherapy is again avoiding the structures associated with salivary production. These include

TABLE 9.2
Summary of dose-volume relationship and constraints above which larynx toxicity is significantly increased

Investigator/ Patients (n)	Critical Organs	Predictive Dose- Volume Parameter	Endpoint
Dornfeld et al (38)/27 patients*	Aryepiglottic folds, pre-epiglottic space, false vocal cords, lateral pharyngeal walls	Point dose <68 Gy	Vocal function
Sanguineti et al (39)/66 patients†	Larynx	V ₅₀ <27%; mean dose <43.5 Gy	Laryngeal edema (fiberoptic examination)
Rancati et al (40)/38 patients‡	Larynx	EUD <30–35 Gy (n = 0.45)	Laryngeal edema (fiberoptic examination)

Abbreviations: EUD = equivalent uniform dose.
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*Twenty-two of 27 patients received chemotherapy plus radiotherapy.
†Twelve of 66 patients received chemotherapy plus radiotherapy.
‡Seven of 38 patients received chemotherapy plus radiotherapy.

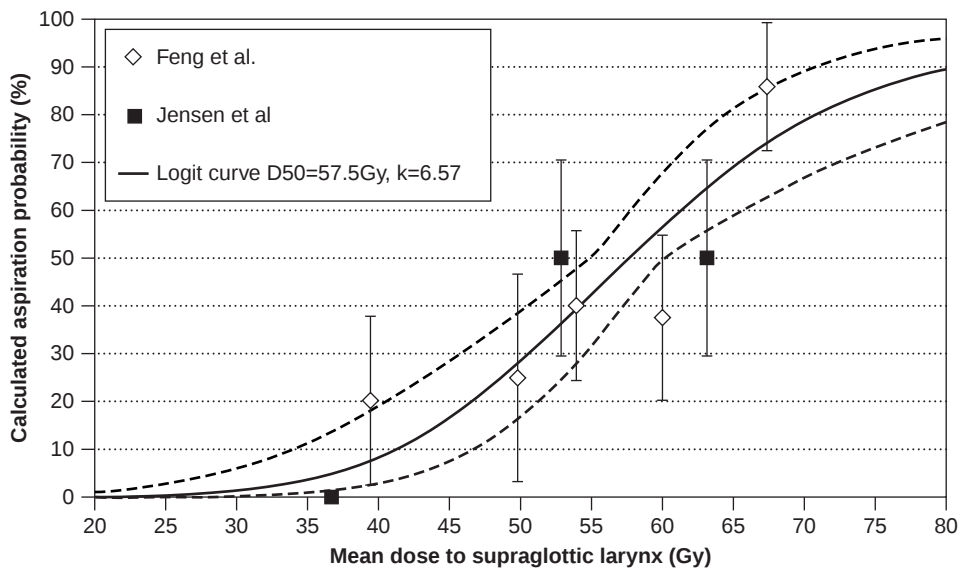


FIGURE 9.1
Dose–effect relationship for dysphagia according to data from Feng et al (35) and Jensen et al (41). Solid line fit to combined data; dotted line fit to 68% confidence area for normal tissue complication probability-logit curve. Reprinted with permission from Ref. 36.

the major parotid, submandibular, sublingual, and minor salivary glands. Avoiding the minor salivary glands is an immensely challenging problem as they can be found throughout the mucosa of the oral cavity and oropharynx, even surrounding the supraglottic laryngeal structures.

Two randomized, controlled trials have compared conventional radiation therapy (RT) with IMRT to prevent xerostomia in patients with early stage nasopharyngeal cancer (42,43). In both these studies, there were improved salivary outcomes in the IMRT group, including increased parotid and whole salivary flow rates. Interestingly, there were no differences detected in patient-reported outcome measures in patients with improved salivary flow between the groups. However, neither article reports outcomes beyond 1 year. It is of concern that there has been a recent report of nodal failures following IMRT for nasopharyngeal carcinoma in regions of parotid suggesting reevaluation of the patients in whom this approach should be attempted (44).

In nonnasopharyngeal primary sites, there is no randomized data to support the use of IMRT for parotid sparing. However, a systematic review was recently published exploring the available data on salivary sparing by the QUANTEC group (45). In this work, a large number of publications on salivary sparing were summarized and combined to provide consensus recommendations. Specifically,

maintaining at least 1 parotid less than 20 Gy or both parotids less than 25 Gy mean dose appears to predict significantly improved salivary flow rates (see Figure 9.2). Moreover, in this review, longer follow-up seems to be associated with slow recovery of salivary function (see Figure 9.3). However, not all patients are suitable for parotid-sparing RT, even with IMRT techniques. Patients with bilateral lymph node involvement and those with nonlateralized tumors may require treatment to the upper lymph nodes bilaterally, thus limiting benefits of IMRT to reduce dose and spare either parotid gland. Submandibular gland sparing has also been shown to be feasible, though given the close proximity of high-risk nodal regions to the glands, it remains experimental (56).

Surgical manipulation of normal tissues may also be employed to improve salivary glands sparing during radiotherapy. Jha et al demonstrated the feasibility of this approach in patients planned for postoperative radiation therapy with conventionally fractionated three-dimensional conformal radiation therapy (57,58). In this technique, the contralateral submandibular gland can be

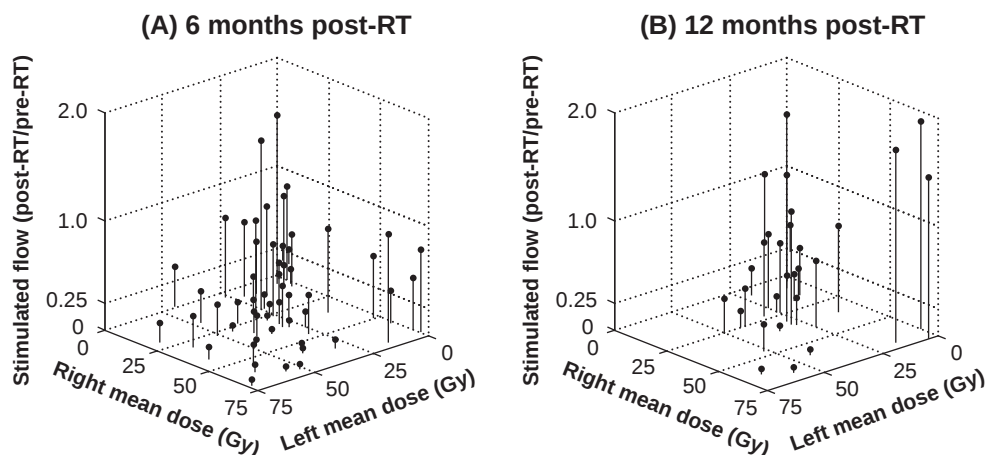
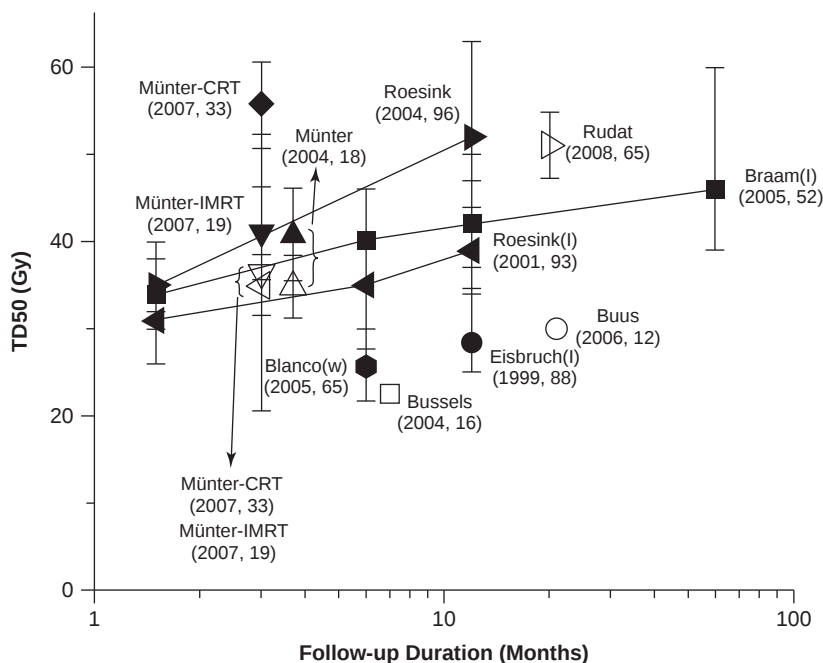


FIGURE 9.2

Stimulated whole mouth salivary measurements versus mean parotid gland dose. Summary of Washington University stimulated salivary results at (A) 6 and (B) 12 months of follow-up. Data showed that when either gland was spared (<20 Gy mean dose), ratio of postradiotherapy to preradiotherapy flow is usually >0.25. Note, if either gland was highly spared (<10-15 Gy), resulting salivary function will usually be high, regardless of irradiation level of the other parotid gland (data originally presented in Blanco et al (46), but redrawn here). Reprinted with permission from Ref. 41.

**FIGURE 9.3**

Reported tissue dose required for 50% response for loss of stimulated saliva flow after radiotherapy (RT) (46–53,55) for single parotid gland. Endpoint considered in reports was salivary flow reduction to below 25% (black symbols) or below 50% (gray symbols) of pretreatment value. Tissue dose required for 50% response defined as dose at which 50% of patients developed complications. Error bars (if shown) indicate 95% confidence intervals; refer to original publications for exact meaning. 95% Confidence intervals for studies by Munter et al (52,53) were estimated from standard errors provided. Lines connect points from data sets with measurements taken at more than one interval after RT. Most studies used salivary gland scintigraphy. Some studies measured physical production (ipsilateral salivary flow or whole salivary flow; marked with "I" or "W," respectively). Data from Buus et al (50) (which did not include preradiotherapy assessments) derived by comparing different regions of parotid gland that had received different doses. Each label gives number of patients. Note, most imaging-derived endpoint data had greater values for tissue dose required for 50% response (TD50) than measured salivary data. CRT, conformal radiotherapy; IMRT, intensity-modulated radiotherapy. Reprinted with permission from Ref. 45. See also Refs. 46,48–55.

repositioned, allowing it to be shielded during subsequent RT as a component of the primary surgical resection. In a randomized comparison of submandibular gland transfer compared with pilocarpine (medical) prevention, there was a significant improvement in the submandibular gland arm at interim analysis leading to early trial stoppage with improved salivary flow and quality of life in the surgical arm (59). When combined with IMRT, further salivary sparing may be feasible (60). However, this technique requires specialized

surgical training and is limited to planned and highly selected postoperative patients.

Evaluation of Dysphagia as an Outcome

A recent systematic review conducted by our laboratory looked specifically at how swallowing outcomes were reported in the literature for head and neck cancer patients after surgery, radiotherapy, and/or chemotherapy (61). Bibliometric methods were used

to identify patterns and trends in the literature. We defined dysphagia broadly as any reported signs or symptoms that would affect swallowing ability, including aspiration, mucositis, or xerostomia. The search resulted in 957 citations, of which 741 were articles reporting original research and underwent full article review. Of these full articles, less than half ($n = 327$) reported dysphagia as either a primary or secondary outcome. Swallowing outcomes were most frequently reported in articles on the combined modality of surgery and radiotherapy ($n = 109$). This was followed by surgery alone ($n = 56$) and chemoradiotherapy ($n = 47$). An encouraging trend, however, was that over time and across geographical regions, there was an increase in frequency of swallowing outcomes reported. The largest proportional increase was for the more recently published chemoradiotherapy articles. Interestingly, during this time, there was also a sudden decrease in articles on surgery alone—likely a reflection of practice changing to favor an increased use of nonsurgical irradiation treatment for early-stage disease and organ-sparing chemoradiation treatment for more advanced disease (62).

Across all years, the most common swallowing outcomes reported related to impairment measures from videofluoroscopic assessments, including physiological variables such as range of motion and timing for oral and pharyngeal movements. Fewer articles reported on swallowing-related function and even fewer reported swallowing-related quality of life. In general, the use of validated swallowing outcome measures in any article was rare, likely a feature of few available standardized dysphagia measures for researchers to use.

Despite the high prevalence of dysphagia and important impact on life quality, the few available dysphagia-specific outcome measures for head and neck cancer patients do not uniformly meet current standards for diagnostic tools (63). Currently, there are five available swallowing-specific outcome measures standardized specifically with head and neck cancer patients. The psychometric features for each of these swallowing outcome measures are detailed in Table 9.3.

A measure with good psychometric properties should, at a minimum, specify a targeted outcome, how the items were derived, and information regarding its reliability and validity. The outcomes targeted typically adhere to the World Health Organization (WHO) taxonomy, which has been available in various iterations since 1980 and is now called the International Classification of Functioning, Disability and Health (ICF) (64). This latest ICF classifies disability and handicap along the same three dimensions of the original WHO version with only a few exceptions: a new taxonomy that is neutral rather than pejorative; incorporates the influences of environmental and personal factors; and details interactions among the three dimensions rather than making them distinct (65,66) (see Figure 9.4). Based on the ICF, therapy is defined as the intervention that “aims to enable people with health conditions experiencing or likely to experience disability to achieve optimal functioning in interaction with the environment” (67).

In comparing and evaluating the evidence to support the clinical use of the available dysphagia-specific outcome measures, it is important to ensure that each measure is stable over time and with different raters. Reliability refers to the degree to which scores are free from errors in measurement (68). Errors in measures may add to the total variance in scores, which reduces the measure’s power to detect statistically significant differences. Comparisons between large groups are more forgiving to error and can be done with less reliable measures than comparisons between individuals. Individual patient tools, as those in Table 9.3, require high internal-consistency reliability (i.e., Cronbach’s alpha coefficients) and high interrater reliability (i.e., Intraclass Correlation Coefficients) ranging from 0.90 to preferably greater than 0.95 (68).

A dysphagia-specific measure is valid for head and neck cancer patients only if it was validated with this patient population (69). Validation studies essentially assess two hypotheses: how well the measure discriminates the dysphagic head and neck cancer patient from similar patients without

dysphagia (i.e., discriminatory validity); and how well the measure relates to other head and neck cancer measures targeting a different outcome assumed to be associated (i.e., criterion and convergent validity) or predictably not associated (i.e., divergent validity) (70). Within these broad categories are many different types of validity tests, and which of these is necessary depends on the purpose of the measure. For example, a measure that captures a swallowing outcome at a single point in time needs, at a minimum, to establish discriminatory validity. In contrast, an evaluative measure aims to capture change in a swallowing outcome over time; therefore, at a minimum, these measures need to establish responsiveness (71). The validation of any measure can be an ongoing process. Over time, measures that were initially validated as discriminatory can be validated for additional purposes (such as evaluative) and/or other patient groups.

Of all five measures specific to swallowing and the head and neck cancer patient, there is one measure for each body functions and structures (72), activities (73), and quality of care (74–76) and two for participation (74–78) (see Table 9.3 on page 186). One of the participation measures also targets function (77). Participation measures represent the patients' perceived disadvantage as it relates to their swallowing physiological function (impairment) and activity (disability). This perceived disadvantage thereby limits or prevents their personal fulfillment and well-being (64). Therefore, the participation outcome as a construct can be captured only from the opinion of patients themselves. The patient perspective is critical in generating items for these measures. Of the swallowing-specific participation measures identified, all appropriately generated items using the patient perspective. Moreover, both measures expanded the patient perspective to also include perspectives from the caregivers (74–76) or clinicians (77), but neither included all three.

To date, there is no available measure that targets medical complications resulting from the presence of dysphagia, such as pneumonia,

malnutrition dehydration, and psychological consequences. Our research group has begun development of such a measure entitled the Medical Outcomes of Dysphagia (MOD) (79,80). At present, the MOD is undergoing reliability and validity analysis for use with head and neck cancer patients

Surgical Dysphagia Treatment

Unfortunately, once dysphagia is established post head and neck cancer treatment there are limited surgical options to regain normal function. In some cases, obstructive defects leading to dysphagia may be removed. In one report, patients with complete hypopharyngeal obstruction thought to be due to mucosal adhesions were treated with an aggressive regimen consisting of recanalization via esophagoscopy and serial dilations in conjunction with intensive swallowing therapy. Of 7 patients treated, 5 had improvements in swallowing, but only 2 improved sufficiently to have gastrostomy tubes removed while maintaining weight (81).

In most cases, the cause of dysphagia is multifactorial and has components of neurologic injury, mucosal anesthesia, and dysregulation of the swallowing process. In these cases, there may be no distinct and surgically amenable lesion. In some cases, complete laryngopharyngectomy followed by transposition of bowel or reconstruction of the pharynx has been attempted when the patient's swallowing function is deemed the factor most contributing to decline in quality of life following treatment. In one series, 12 patients with significant dysphagia secondary to stricture or fistula following cancer treatment were reconstructed using bowel transposition (82). There were no deaths, and a majority of patients were able to resume oral food intake, though some were able to tolerate only liquids. The serious nature of salvage procedures for iatrogenic dysphagia clearly indicates the need to identify risk factors predictive of dysphagia in advance of attempts at organ-sparing treatment.

Tools	Outcome	Perspective	Domains (Themes)
Performance Status Scale for Head and Neck Cancer (PSS-HN) (73)	Speech and Swallowing Activities	Items generated by clinicians Tool completed by clinicians	Eating (eating in public, normalcy of diet) Speech (understandability of speech)
MD Anderson Dysphagia Inventory (MDADI) (77)	Swallowing Activities and Participation	Items generated by clinicians and patients Tool completed by patients	Psychosocial (global, emotional, functional, physical)
Swallowing Quality of Life (SWAL-QOL) (74–76, 78)	Swallowing Body Function and Structures	Items generated by patients and caregivers Tool completed by patients	Psychosocial (food selection, burden, mental health, social functioning, fear, eating duration, eating desire, communication, sleep, fatigue)

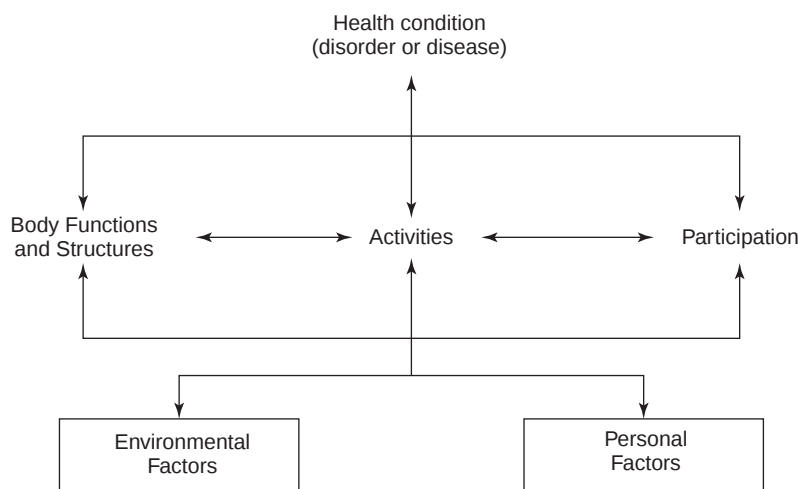
Validation Population	Test-retest Reliability	Validity
181 adult cancer patients of the oral cavity (28%), pharynx (36%), larynx (29%), and other head and neck areas (7%)	Public subscale: Kappa = 0.78 (SE = 0.11) Normalcy subscale: Kappa = 0.88 (SE = 0.08) Understandability Subscale: Kappa = 0.64 (SE = 0.08)	Differentiated patients with head and neck cancer from breast cancer on all 3 subscales ($P < .001$) Severity of all subscales aligned with extent of surgery ($P < .02$)
100 adult cancer patients of the oral cavity (12%), oropharynx (8%), hypopharynx (6%), larynx (64%), and other head and neck areas (10%)	Global subscale ^a : 0.69 Emotional subscale: 0.88 Functional subscale: 0.88 Physical subscale: 0.86	Moderately correlated with all PSS-HN subscales ($r_s = 0.47-0.61$) Moderately correlated with all 36-Item Short Form Health Survey (SF-36) subscales ($r_s = 0.21-0.54$) Severity of all subscales aligned with extent of surgery ($P < .001$)
386 adult outpatients with mixed etiologies including cancer (28%), vascular (16%), degenerative neurological (13%), other neurological (9%), respiratory (6%), trauma (4%), chronic medical (4%), dementia (1%), other (7%), and unknown (12%)	Food selection subscale: $r = 0.83$ Burden subscale: $r = 0.60$ Mental health subscale: $r = 0.80$ Social functioning subscale: $r = 0.88$ Fear subscale: $r = 0.74$ Eating duration subscale: $r = 0.64$ Eating desire subscale: $r = 0.91$ Communication subscale: $r = 0.76$ Sleep subscale: $r = 0.80$ Fatigue subscale: $r = 0.85$	Differentiated patients with dysphagia and no dysphagia on all subscales ($P < .000$) Differentiated patients fed by tube and no tube on 6 subscales (food selection, burden, mental health, social functioning, fear, eating desire) ($P < .003$) Severity of all subscales aligned with degree of solid food restriction ($P < .0001$) Severity of 2 subscales (burden, social functioning) aligned with degree of liquid restriction ($P < .000$) Severity of all subscales aligned with degree of oral or pharyngeal impairment ($P < .0001$)

(continued)

TABLE 9.3 Continued

Tools	Outcome	Perspective	Domains (Themes)
Swallowing Quality of Care (SWAL-CARE) (74–76)	Swallowing Quality of Care	Items generated by patients and caregivers Tool completed by patients	Care (clinical information, general advice, patient satisfaction)
Modified Barium Swallow Measure of Impairment (MBSImp) (72)	Swallowing Body Function and Structures	Items generated by clinicians	Physiology of swallowing (lip closure, tongue control, mastication, lingual motion, oral residue, initiation of pharyngeal swallow, soft palate elevation, laryngeal elevation, hyoid movement, epiglottic movement, laryngeal closure, pharyngeal stripping wave, pharyngeal contraction, PES opening, tongue base retraction, pharyngeal residue, esophageal clearance in the upright position.

Validation Population	Test-retest Reliability	Validity
386 adult outpatients with mixed etiologies including cancer (28%), vascular (16%), degenerative neurological (13%), other neurological (9%), respiratory (6%), trauma (4%), chronic medical (4%), dementia (1%), other (7%), and unknown (12%)	Clinical subscale: $r = 0.83$ General: $r = 0.60$ Satisfaction subscale: $r = 0.80$	Differentiated patients with mdysphagia and no dysphagia on all subscales ($P < .000$) Did not differentiate patients fed by tube and no tube on any subscale ($P > 2$) Severity of 2 subscales (general, satisfaction) aligned with degree of solid food restriction ($P < .08$) Severity of subscales did not align with degree of liquid restriction ($P > 1$) Severity of all subscales aligned with degree of pharyngeal impairment ($P < .02$) Severity of 1 subscale (satisfaction) aligned with degree of oral impairment ($P < .03$)
300 adult patients with mixed etiologies including pulmonary (23%), HNC (21%), neurology (16%), gastroenterology (12%), cardiothoracic (9%), general otolaryngology (5%), neurosurgery (3%), oncology other than HNC (3%), general practice (3%), endocrine (2%), orthopedics (1%), trauma (1%), general surgery (1%), rheumatology (1%), vascular (1%), and unknown/unreported (1%)	Raters were specially trained speech-language pathologists who achieved a minimum of 80% agreement (measured as % of exact agreement) for intrarater and interrater agreement with an established standard.	Oral impairment components correlated poorly with Penetration and Aspiration Scale (85) ($r = 0.27$, $R^2 = 0.07$, $P < .0005$); moderately with dietary recommendations ($r = 0.47$, $R^2 = 0.22$, $P < .0005$); poorly with BMI ($r = -0.08$, $R^2 = 0.02$, $P < .20$); poorly with PG-SGA ($r = 0.28$, $R^2 = 0.08$, $P < .0005$); poorly with SF-36 ($r = 0.17$, $R^2 = 0.03$, $P < .04$); poorly with SWAL-QOL Eating Duration ($r = -0.24$, $R^2 = 0.06$, $P < .003$); Food Selection ($r = -0.03$, $R^2 = 0.08$, $P < .001$); Communication ($r = -0.34$, $R^2 = 0.12$, $P < .0005$); Social Functioning ($r = -0.26$, $R^2 = 0.07$, $P < .002$) Pharyngeal impairment components correlated poorly with Penetration and Aspiration Scale ($r = 0.22$, $R^2 = 0.05$, $P < .0005$); moderately with dietary recommendations ($r = 0.54$, $R^2 = 0.29$, $P < .0005$); poorly with BMI ($r = -0.21$, $R^2 = 0.04$, $P < .0005$); poorly with PG-SGA ($r = 0.20$, $R^2 = 0.04$, $P < .008$); poorly with SF-36 ($r = 0.16$, $R^2 = 0.03$, $P < .046$); poorly with SWAL-QOL General Burden ($r = -0.21$, $R^2 = 0.04$, $P < .01$); Food Selection ($r = -0.19$, $R^2 = 0.04$, $P < .024$); Communication ($r = -0.32$, $R^2 = 0.10$, $P < .0005$); Social Functioning ($r = -0.25$, $R^2 = 0.07$, $P < .002$)

**FIGURE 9.4**

Interactions Between the Components of ICF. Reprinted with permission from Ref. 65.

Behavioral Dysphagia Therapy

Therapy for the head and neck cancer patient begins with a good understanding of the swallow anatomy followed by a comprehensive evaluation of the swallow physiology. Swallowing physiology is typically assessed both clinically at bedside and instrumentally using either videofluoroscopy or fiberoptic endoscopy. Ultimately, the main purpose of behavioral dysphagia therapy is to improve the swallow so to facilitate safe (no aspiration) and efficient bolus transport through the oral cavity, pharynx, and esophagus (83). By so doing, therapy ultimately aims to prevent aspiration pneumonia, malnutrition, dehydration, anxiety, and depression—all of which are serious comorbidities in patients with dysphagia (84).

As a precursor to initiating more formal dysphagia therapy, it is important to prepare patients properly for the possibility that their dysphagia may not improve, may worsen, or that their cancer treatment may cause dysphagia if it was not already present. Typically, this is achieved through educational sessions after the diagnosis of cancer has been confirmed but before the cancer treatment begins. Patients who are poorly prepared

for their swallowing problems are at higher risk to become anxious with their failed attempts to eat by mouth. This in turn can lead to food avoidances and eventually malnutrition (79). As part of the education process, patients may also be provided with strategies or exercises to prevent or reduce the severity of the developing dysphagia. Current research is assessing the benefits of these pretreatment swallowing exercises on swallowing function after chemoradiation (86).

A well-designed formal behavioral swallowing therapy regime takes into consideration the anticipated effects of the various cancer treatments, often times administered in combination. For example, therapy for surgical patients typically starts approximately 5 to 10 days following surgery or as soon as the surgeon indicates that the patient has healed sufficiently. In contrast, patients receiving chemoradiation may receive swallowing therapy during their cancer treatment, but often their participation is limited by oral pain from treatment side effects such as fatigue or mucositis. In addition, unlike surgical patients whose swallow generally improves over time, there is emerging evidence that the ill effects of chemoradiation on swallow physiology

may not be realized immediately but instead manifest over time. Therefore, patients receiving chemoradiation should be followed for their swallowing ability even years after treatment has ended so that, if necessary, swallowing therapy may be offered.

Compensatory swallowing strategies are typically introduced early during videofluoroscopic assessment of swallowing physiology. These treatment strategies do not directly aim to improve the swallow physiology but instead aim to redirect or improve bolus flow and/or eliminate patient symptoms (83). In order to be of benefit, a compensatory strategy must be executed correctly and during every swallow. Examples of compensatory strategies include posturing of the head and neck, techniques to improve oral sensory awareness, diet modification, swallowing maneuvers, and intraoral prosthetics.

Postural Techniques

The first compensatory strategy attempted with head and neck cancer patients is postural techniques. Patients who are candidates for these strategies are those who can follow direction and have good movement of the head and neck. A common postural technique is rotation of the head to the damaged or weakened pharynx serving to direct the bolus through the unimpaired pharynx. Likewise, a head tilt to the unimpaired oral cavity uses gravitational forces to direct the bolus through this unimpaired side. Other postures include chin tuck, head back, and upper torso tilt.

Techniques to Improve Sensory Awareness

Sensory feedback strategies are typically administered simultaneously with food introduction. They aim to increase bolus awareness, thereby decreasing any delays in bolus transit times (e.g., the trigger of the pharyngeal swallow). One such technique involves increasing downward pressure of the spoon against the tongue when presenting food in the mouth. Other common sensory strategies include chilled

foods, sour tasting foods or liquids, and larger bolus volumes.

Food Consistency Changes

A common diet modification includes thickening liquids so that they flow through the pharynx at a slower rate, thereby compensating for delays in the trigger of the pharyngeal swallow. Pureeing solids might also be prescribed for patients with trismus or limited mastication ability. Diet modifications that eliminate certain food textures from a patient's diet should be one of the last compensatory strategies considered (83). Generally, elimination of certain foods such as thin liquids or solids from the diet can have serious side effects for the patient. Emotionally, these patients are at high risk for depression and anxiety, as medically they are at high risk for dehydration and malnutrition (79).

Swallowing Maneuvers

Swallowing maneuvers are based on what we know about normal swallow physiology. Their intent is to compensate for impaired coordination of swallowing and respiration. One example is the supraglottic swallow maneuver. This maneuver aims to duplicate a functional swallow by adducting the vocal folds to intentionally cease respiration just before and during the swallow. Likewise, the Mendelsohn maneuver is administered to patients with impaired UES opening. This maneuver facilitates greater anterior and superior hyolaryngeal movement, thereby attempting to compensate for impairments in duration and range of UES opening.

Intraoral Prosthetic

Prosthetic devices are used to compensate for oropharyngeal structures that were either ablated or altered during surgery. A palatal lift, for example, serves to lift the existing velum toward the posterior pharyngeal wall, thereby helping to prevent nasal regurgitation. Likewise, an obturator serves to fill the palatal gap in patients where the velum was surgically removed. Other devices augment the maxilla by lowering or reshaping it to allow for better contact with the tongue during oral bolus transport.

These devices are especially useful in patients whose surgical ablation included the tongue.

In addition to compensatory strategies, there are active therapy strategies that aim to facilitate remediation of the impaired swallow physiology (87). These include range of motion and resistance exercises. Each exercise is designed to target a specific muscle or muscle groups. Some clinicians have introduced these exercises before the start of chemoradiation cancer treatment aiming to prevent or decrease the severity of the swallowing impairment before they develop. These exercises can be done with the lips, tongue, jaw, and larynx.

Oral movements should be encouraged at all times—be it in a structured active oral exercise regime (as described above) or simply during normal intake of food and liquids. For this reason, clinicians now discourage a nil-per-os recommendation especially for patients undergoing radiotherapy or chemoradiotherapy. During the course of these treatments, patients should instead be encouraged to maintain oral intake for as long and as much as they can tolerate (28). The premise here is that neural circuits that do not actively engage in tasks for an extended period of time begin to degrade. This is more commonly referred to as the “use it or lose it” principle of physical rehabilitation (88).

Two well-conducted systematic reviews have recently been completed to evaluate the effectiveness of compensatory and active therapy interventions specific for dysphagia secondary to head and neck cancer (89,90). They each conclude that, although some significant outcome studies have been published, most research assessing the benefits of various compensatory treatments are based on small sample sizes and have suboptimal study design. For these reasons, much remains to be learned about the best swallowing therapy for these patients. Future research is therefore needed using rigorous and properly controlled study designs, such as randomized controlled trials, to assess for the relative benefit of these treatments. Some of this research is already underway, and we look forward to their upcoming results.

■ CONCLUSIONS

Swallowing is a complex process that depends on a series of precisely coordinated biomechanical events. If disrupted by the head and neck cancer or its treatment, the effects can be seen at any outcome level: body function, activity, and/or participation. Fortunately, there is emerging evidence that careful treatment selection and appropriate swallowing rehabilitation can reduce the impact of dysphagia in the head and neck cancer patient.

■ REFERENCES

1. Eisbruch A, Lyden T, Bradford CR, et al. Objective assessment of swallowing dysfunction and aspiration after radiation concurrent with chemotherapy for head-and-neck cancer. *Int J Radiat Oncol Biol Phys*. 2002;53:23–28.
2. Logemann JA, Rademaker AW, Pauloski BR, et al. Site of disease and treatment protocol as correlates of swallowing function in patients with head and neck cancer treated with chemoradiation. *Head Neck*. 2006;28:64–73.
3. Cunningham ETJ, Donner MW, Point S. Anatomical and physiological overview. In: Jones B, Donner MW, eds. *Normal and Abnormal Swallowing: Imaging in Diagnosis and Therapy*. New York, NY: Springer-Verlag; 1991:7–32.
4. Dodds WJ. Physiology of swallowing. *Dysphagia*. 1989;3:171–178.
5. Jafari S, Prince RA, Kim DY, Paydarfar D. Sensory regulation of swallowing and airway protection: a role for the internal superior laryngeal nerve in humans. *J Physiol*. 2003;550:287–304.
6. Rhodus NL, Moller K, Colby S, Bereuter J. Dysphagia in patients with three different etiologies of salivary gland dysfunction. *Ear Nose Throat J*. 1995;74:39–48.
7. Dodds WJ, Stewart ET, Logemann JA. Physiology and radiology of the normal oral and pharyngeal phases of swallowing. *AJR Am J Roentgenol*. 1990;154:953–963.
8. McConnel FM. Analysis of pressure generation and bolus transit during pharyngeal swallowing. *Laryngoscope*. 1988;98:71–78.
9. Jean A. Brainstem control of swallowing: localization and organization of the central pattern generator for swallowing. In: Taylor A, ed. *Neurophysiology of the*

- Jaws and Teeth*. Houndmills, Basingstoke, England: MacMillan Press; 1990.
10. Jean A, Kessler J-P, Tell F. Nucleus tractus solitarii and deglutition: monoamines, excitatory amino acids, and cellular properties. In: Baracco RA, ed. *Nucleus of the Solitary Tract*. Boca Raton, FL: CRC Press; 1994.
 11. Ward EC, Bishop B, Frisby J, Stevens M. Swallowing outcomes following laryngectomy and pharyngolaryngectomy. *Arch Otolaryngol Head Neck Surg*. 2002;128:181–186.
 12. Pauloski BR, Rademaker AW, Logemann JA, et al. Surgical variables affecting swallowing in patients treated for oral/oropharyngeal cancer. *Head Neck*. 2004;26:625–636.
 13. Ding R, Logemann JA. Swallow physiology in patients with trach cuff inflated or deflated: a retrospective study. *Head Neck*. 2005;27:809–813.
 14. O'Connell DA, Reiger J, Dziegielewski PT, et al. Effect of lingual and hypoglossal nerve reconstruction on swallowing function in head and neck surgery: prospective functional outcomes study. *J Otolaryngol Head Neck Surg*. 2009;38:246–254.
 15. Lewin JS, Barringer DA, May AH, et al. Functional outcomes after laryngopharyngectomy with anterolateral thigh flap reconstruction. *Head Neck*. 2006;28:142–149.
 16. Hsiao HT, Leu YS, Chang YC, Yang JC, Tung KY. Voice and swallowing after laryngopharyngectomy and free ileocolic flap reconstruction for hypopharyngeal cancer. *Ann Plast Surg*. 2009;62:390–394.
 17. Chien CY, Su CY, Hwang CF, Chuang HC, Jeng SF, Chen YC. Ablation of advanced tongue or base of tongue cancer and reconstruction with free flap: functional outcomes. *Eur J Surg Oncol*. 2006;32:353–357.
 18. Fu KK, Pajak TF, Trotti A, et al. A Radiation Therapy Oncology Group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: first report of RTOG 9003. *Int J Radiat Oncol Biol Phys*. 2000;48:7–16.
 19. Langerman A, Maccracken E, Kasza K, Haraf DJ, Vokes EE, Stenson KM. Aspiration in chemoradiated patients with head and neck cancer. *Arch Otolaryngol Head Neck Surg*. 2007;133:1289–1295.
 20. Garden AS, Harris J, Trotti A, et al. Long-term results of concomitant boost radiation plus concurrent cisplatin for advanced head and neck carcinomas: a phase II trial of the radiation therapy oncology group (RTOG 99-14). *Int J Radiat Oncol Biol Phys*. 2008;71:1351–1355.
 21. Adelstein DJ, Li Y, Adams GL, et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. *J Clin Oncol*. 2003;21:92–98.
 22. Forastiere AA, Goepfert H, Maor M, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *N Engl J Med*. 2003;349:2091–2098.
 23. Bourhis J, Overgaard J, Audry H, et al. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. *Lancet*. 2006;368:843–854.
 24. Machtay M, Moughan J, Trotti A, et al. Factors associated with severe late toxicity after concurrent chemoradiation for locally advanced head and neck cancer: an RTOG analysis. *J Clin Oncol*. 2008;26:3582–3589.
 25. Mittal BB, Pauloski BR, Haraf DJ, et al. Swallowing dysfunction—preventative and rehabilitation strategies in patients with head-and-neck cancers treated with surgery, radiotherapy, and chemotherapy: a critical review. *Int J Radiat Oncol Biol Phys*. 2003;57:1219–1230.
 26. Staar S, Rudat V, Stuetzer H, et al. Intensified hyperfractionated accelerated radiotherapy limits the additional benefit of simultaneous chemotherapy—results of a multicentric randomized German trial in advanced head-and-neck cancer. *Int J Radiat Oncol Biol Phys*. 2001;50:1161–1171.
 27. Lewin JS. Speech and swallowing following treatment for oral cancer. In: Werning JW, ed. *Oral Cancer*. New York, NY: Thieme Medical Publishers; 2007:304–308.
 28. Platteaux N, Dirix P, Dejaeger E, Nuyts S. Dysphagia in head and neck cancer patients treated with chemoradiotherapy. *Dysphagia*. 2009;25:139–152.
 29. Smith RV, Kotz T, Beitler JJ, Wadler S. Long-term swallowing problems after organ preservation therapy with concomitant radiation therapy and intravenous hydroxyurea: initial results. *Arch Otolaryngol Head Neck Surg*. 2000;126:384–389.
 30. Dirix P, Nuyts S, Van den Bogaert W. Radiation-induced xerostomia in patients with head and neck cancer: a literature review. *Cancer*. 2006;107:2525–2534.
 31. Hamlet S, Faull J, Klein B, et al. Mastication and swallowing in patients with postirradiation xerostomia. *Int J Radiat Oncol Biol Phys*. 1997;37:789–796.
 32. Rhodus NL, Moller K, Colby S, Bereuter J. Articulatory speech performance in patients with salivary gland dysfunction: a pilot study. *Quintessence Int*. 1995;26:805–810.
 33. Ringash J, Warde P, Lockwood G, O'Sullivan B, Waldron J, Cummings B. Postradiotherapy quality

- of life for head-and-neck cancer patients is independent of xerostomia. *Int J Radiat Oncol Biol Phys.* 2005; 61:1403–1407.
34. Eisbruch A, Schwartz M, Rasch C, et al. Dysphagia and aspiration after chemoradiotherapy for head-and-neck cancer: which anatomic structures are affected and can they be spared by IMRT? *Int J Radiat Oncol Biol Phys.* 2004;60:1425–1439.
 35. Feng FY, Kim HM, Lyden TH, et al. Intensity-modulated radiotherapy of head and neck cancer aiming to reduce dysphagia: early dose-effect relationships for the swallowing structures. *Int J Radiat Oncol Biol Phys.* 2007;68:1289–1298.
 36. Rancati T, Schwarz M, Allen AM, et al. Radiation dose-volume effects in the larynx and pharynx. *Int J Radiat Oncol Biol Phys.* 2010;76:S64–S69.
 37. Langendijk JA, Doornaert P, Rietveld DH, Verdonck-de Leeuw IM, Rene Leemans C, Slotman BJ. A predictive model for swallowing dysfunction after curative radiotherapy in head and neck cancer. *Radiother Oncol.* 2009;90:189–195.
 38. Dornfeld K, Simmons JR, Karnell L, et al. Radiation doses to structures within and adjacent to the larynx are correlated with long-term diet and speech-related quality of life. *Int J Radiat Oncol Biol Phys.* 2007;68:750–757.
 39. Sanguineti G, Adapala P, Endres EJ, et al. Dosimetric predictors of laryngeal edema. *Int J Radiat Oncol Biol Phys.* 2007;68:741–749.
 40. Rancati T, Sanguineti G, Fiorino C. NTCP modeling of sub-acute/late laryngeal edema scored by fiberoptic examination: Evidence of a large volume effect. *Int J Radiat Oncol Biol Phys.* 2007;69(Suppl 3):S409–S410.
 41. Jensen K, Lambertsen K, Grau C. Late swallowing dysfunction and dysphagia after radiotherapy for pharynx cancer: frequency, intensity, and correlation with dose and volume parameters. *Radiother Oncol.* 2007;85:74–82.
 42. Kam MK, Leung SF, Zee B, et al. Prospective randomized study of intensity-modulated radiotherapy on salivary gland function in early-stage nasopharyngeal carcinoma patients. *J Clin Oncol.* 2007;25:4873–4879.
 43. Pow EH, Kwong DL, McMillan AS. Xerostomia and quality of life after intensity-modulated radiotherapy vs. conventional radiotherapy for early-stage nasopharyngeal carcinoma: initial report on a randomized controlled clinical trial. *Int J Radiat Oncol Biol Phys.* 2006;66:981–991.
 44. Cannon DM, Lee NY. Recurrence in region of spared parotid gland after definitive intensity-modulated radiotherapy for head and neck cancer. *Int J Radiat Oncol Biol Phys.* 2008;70:660–665.
 45. Deasy JO, Moiseenko V, Marks L, Chao KSC, Nam J, Eisbruch A. Radiotherapy dose-volume effects on salivary gland function. *Int J Radiat Oncol Biol Phys.* 2010;76:S58–S63.
 46. Blanco AI, Chao KS, El Naqa I, et al. Dose-volume modeling of salivary function in patients with head-and-neck cancer receiving radiotherapy. *Int J Radiat Oncol Biol Phys.* 2005;62:1055–1069.
 47. Roesink JM, Moerland MA, Battermann JJ, et al. Quantitative dose–volume response analysis of changes in parotid gland function after radiotherapy in the head-and-neck region. *Int J Radiat Oncol Biol Phys.* 2001;51:938–946.
 48. Braam P, Roesink J, Raaijmakers C, Busschers W, Terhaard C. Quality of life and salivary output in patients with head-and-neck cancer five years after radiotherapy. *Radiat Oncol.* 2007;2:3.
 49. Bussels B, Maes A, Flamen P, et al. Dose-response relationships within the parotid gland after radiotherapy for head and neck cancer. *Radiother Oncol.* 2004;73:297–306.
 50. Buus S, Grau C, Munk OL, et al. Individual radiation response of parotid glands investigated by dynamic ¹¹C-methionine PET. *Radiother Oncol.* 2006;78:262–269.
 51. Eisbruch A, Kim HM, Terrell JE, Marsh LH, Dawson LA, Ship JA. Xerostomia and its predictors following parotid-sparing irradiation of head-and-neck cancer. *Int J Radiat Oncol Biol Phys.* 2001;50:695–704.
 52. Münter MW, Karger CP, Hoffner SG, et al. Evaluation of salivary gland function after treatment of head-and-neck tumors with intensity-modulated radiotherapy by quantitative pertechnetate scintigraphy. *Int J Radiat Oncol Biol Phys.* 2004;58:175–184.
 53. Münter MW, Hoffner S, Hof H, et al. Changes in salivary gland function after radiotherapy of head and neck tumors measured by quantitative pertechnetate scintigraphy: comparison of intensity-modulated radiotherapy and conventional radiation therapy with and without Amifostine. *Int J Radiat Oncol Biol Phys.* 2007;67:651–659.
 54. Roesink JM, Moerland MA, Hoekstra A, Rijk PPV, Terhaard CHJ. Scintigraphic assessment of early and late parotid gland function after radiotherapy for head-and-neck cancer: a prospective study of dose-volume response relationships. *Int J Radiat Oncol Biol Phys.* 2004;58:1451–1460.
 55. Rudat V, Münter M, Rades D, et al. The effect of amifostine or IMRT to preserve the parotid function after radiotherapy of the head and neck region measured by quantitative salivary gland scintigraphy. *Radiother Oncol.* 2008;89:71–80.

56. Saarilahti K, Kouri M, Collan J, et al. Sparing of the submandibular glands by intensity modulated radiotherapy in the treatment of head and neck cancer. *Radiother Oncol.* 2006;78:270–275.
57. Jha N, Seikaly H, Harris J, et al. Prevention of radiation induced xerostomia by surgical transfer of submandibular salivary gland into the submental space. *Radiother Oncol.* 2003;66:283–289.
58. Jha N, Seikaly H, McGaw T, Coulter L. Submandibular salivary gland transfer prevents radiation-induced xerostomia. *Int J Radiat Oncol Biol Phys.* 2000;46:7–11.
59. Jha N, Seikaly H, Harris J, et al. Phase III randomized study: oral pilocarpine versus submandibular salivary gland transfer protocol for the management of radiation-induced xerostomia. *Head Neck.* 2009;31:234–243.
60. Saibishkumar EP, Jha N, Scrimger RA, et al. Sparing the parotid glands and surgically transferred submandibular gland with helical tomotherapy in post-operative radiation of head and neck cancer: a planning study. *Radiother Oncol.* 2007;85:98–104.
61. Tran E, Reichardt B, Martino R. *Mapping Swallowing Outcomes in the Head and Neck Cancer Literature.* Poster session presented at: International Conference on Reconstructive Preprosthetic Surgery: April 16, 2007; Charleston, SC.
62. Shah JP, Karnell LH, Hoffman HT, et al. Patterns of care for cancer of the larynx in the United States. *Arch Otolaryngol Head Neck Surg.* 1997;123:475–483.
63. Jaeschke R, Guyatt G, Sackett DL. Users' guides to the medical literature. III. How to use an article about a diagnostic test. A. Are the results of the study valid? Evidence-Based Medicine Working Group. *JAMA.* 1994;271:389–391.
64. World Health Organization. *International Classification of Impairments, Activities and Participation: A Manual of Dimensions of Disablement and Functioning.* Geneva, Switzerland: World Health Organization; 1997.
65. World Health Organization. *International Classification of Functioning, Disability, and Health.* Geneva, Switzerland: World Health Organization; 2001:18.
66. Meyers AR, Andresen EM, Hagglund KJ. A model of outcomes research: spinal cord injury. *Arch Phys Med Rehabil.* 2000;81:S81–S90.
67. Stucki G, Cieza A, Melvin J. The International Classification of Functioning, Disability and Health (ICF): a unifying model for the conceptual description of the rehabilitation strategy. *J Rehabil Med.* 2007;39:279–285.
68. Nunnally JC, Bernstein IH. *Psychometric Theory.* Toronto, ON: McGraw-Hill, Inc.; 1994.
69. Meyer GJ. Guidelines for reporting information in studies of diagnostic test accuracy: the STARD initiative. *J Pers Assess.* 2003;81:191–193.
70. Streiner DL, Norman GR. *Health Measurement Scales: A Practical Guide to Their Development and Use.* New York, NY: Oxford University Press; 2003.
71. Beaton DE, Bombardier C, Katz JN, Wright JG. A taxonomy for responsiveness. *J Clin Epidemiol.* 2001;54:1204–1217.
72. Martin-Harris B, Brodsky MB, Michel Y, et al. MBS measurement tool for swallow impairment—MBSImp: establishing a standard. *Dysphagia.* 2008; 23:392–405.
73. List MA, Ritter-Sterr C, Lansky SB. A performance status scale for head and neck cancer patients. *Cancer.* 1990;66:564–569.
74. McHorney CA, Bricker DE, Kramer AE, et al. The SWAL-QOL outcomes tool for oropharyngeal dysphagia in adults: I. Conceptual foundation and item development. *Dysphagia.* 2000;15:115–121.
75. McHorney CA, Bricker DE, Robbins J, Kramer AE, Rosenbek JC, Chignell KA. The SWAL-QOL outcomes tool for oropharyngeal dysphagia in adults: II. Item reduction and preliminary scaling. *Dysphagia.* 2000;15:122–133.
76. McHorney CA, Robbins J, Lomax K, et al. The SWAL-QOL and SWAL-CARE outcomes tool for oropharyngeal dysphagia in adults: III. Documentation of reliability and validity. *Dysphagia.* 2002;17:97–114.
77. Chen AY, Frankowski R, Bishop-Leone J, et al. The development and validation of a dysphagia-specific quality-of-life questionnaire for patients with head and neck cancer: the M. D. Anderson dysphagia inventory. *Arch Otolaryngol Head Neck Surg.* 2001;127:870–876.
78. McHorney CA, Martin-Harris B, Robbins J, Rosenbek J. Clinical validity of the SWAL-QOL and SWAL-CARE outcome tools with respect to bolus flow measures. *Dysphagia.* 2006;21:141–148.
79. Martino R, Beaton D, Diamant NE. Perceptions of psychological issues related to dysphagia differ in acute and chronic patients. *Dysphagia.* 2010;25:26–34.
80. Martino R, Silver F, Newman A, Perera J, Chakraporty SJ, Mikilus D. The usefulness of a national stroke registry to derive predictors for dysphagia [abstract]. *Dysphagia.* 2007;22:402.
81. Franzmann EJ, Lundy DS, Abitbol AA, Goodwin WJ. Complete hypopharyngeal obstruction by mucosal adhesions: a complication of intensive chemoradiation for advanced head and neck cancer. *Head Neck.* 2006;28:663–670.

82. Hester TR, McConnel F, Nahai F, Cunningham SJ, Jurkiewicz MJ. Pharyngoesophageal stricture and fistula. Treatment by free jejunal graft. *Ann Surg.* 1984;199:762–769.
83. Logemann JA. Rehabilitation of the head and neck cancer patient. *Semin Oncol.* 1994;21:359–365.
84. Martino R, Beaton D, Diamant NE. Using different perspectives to generate items for a new scale measuring medical outcomes of dysphagia (MOD). *J Clin Epidemiol.* 2009;62:518–526.
85. Rosenbek JC, Robbins JA, Roecker EB, Coyle JL, Wood JL. A penetration-aspiration scale. *Dysphagia.* 1996;11:93–98.
86. Carroll WR, Locher JL, Canon CL, Bohannon IA, McColloch NL, Magnuson JS. Pretreatment swallowing exercises improve swallow function after chemoradiation. *Laryngoscope.* 2008;118:39–43.
87. Lazarus C. Tongue strength and exercise in healthy individuals and in head and neck cancer patients. *Semin Speech Lang.* 2006;27:260–267.
88. Kleim JA, Jones TA. Principles of experience-dependent neural plasticity: implications for rehabilitation after brain damage. *J Speech Lang Hear Res.* 2008;51:S225–S239.
89. McCabe D, Ashford J, Wheeler-Hegland K, et al. Evidence-based systematic review: oropharyngeal dysphagia behavioral treatments. Part IV—impact of dysphagia treatment on individuals' postcancer treatments. *J Rehabil Res Dev.* 2009;46:205–214.
90. Speyer R, Baijens L, Heijnen M, Zwijnenberg I. Effects of therapy in oropharyngeal dysphagia by speech and language therapists: a systematic review. *Dysphagia.* 2009;25:40–65.

CHAPTER 10

Functional Imaging of Head and Neck Cancer with Positron Emission Tomography

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■ INTRODUCTION

Accurate staging and restaging of head and neck cancer (HNC) is important to clinical practice because of its prognostic implications, role in tailoring treatment, and assistance with avoidance of futile aggressive therapies in the case of incurable disease (1).

Conventional work-up, consisting of physical examination, panendoscopy, biopsy, and structural imaging, such as computerized axial tomography (CT) and/or magnetic resonance imaging (MRI), provide much of the information in current use for clinical staging.

Although ultrasound, CT, and MRI provide important structural information, they do have limitations, which include the inability to define disease in morphologically normal nodes measuring less than 1 cm. Further, these modalities can be limited in their ability to distinguish between tumor and surrounding tissues when normal tissue planes are disrupted. This is a problem of particular relevance in the post treatment setting where distinction between potential residual tumor and surrounding edema, inflammation, and fibrosis is required. Image-guided fine needle aspiration and cytology or biopsy are useful if able to confirm

recurrent/residual disease but less so if negative or inconclusive.

Fluorine-18-fluoro-2-deoxy-D-glucose (F-18 FDG) positron emission tomography (PET) is a functional imaging tool that provides incremental diagnostic information through improved tumor delineation by virtue of increased metabolic activity of tumor cells, without relying on the presence of structural abnormality (2–7).

In addition, the use of tracers other than FDG combined with PET is now providing the ability to biologically characterize tumor with the potential to supply early prognostic information and guide the use of targeted therapies (8–10).

This chapter discusses the role of PET in the management of mucosal head and neck squamous cell carcinoma (HNSCC) including nasopharyngeal carcinoma (NPC) along with its potential clinical role in the biological characterization of tumor.

■ PRINCIPLES OF PET

PET provides an assessment of physiological and biochemical processes by way of tissue uptake and retention of radiopharmaceuticals that decay by releasing a positron to achieve a more stable state.

These positron-emitting radionuclides are generally produced in a cyclotron through bombardment of nonradioactive chemicals with charged particles that are accelerated in an alternating magnetic field and then extracted onto a target material. This process creates nuclei with a relative excess of protons to neutrons. Over a time course measuring seconds to several days, these radionuclides decay with a physical half-life that is characteristic of the atom produced. The emitted positron collides with an electron, and the mass of each is converted to energy in the form of a pair of photons that are ejected from the point of annihilation in opposite directions.

The PET scanner detects these annihilation photons and, through their temporal coincidence, determines their point of origin within the body. By reconstructing the locations of millions of such events, the scanner can derive a series of images for clinical interpretation.

In clinical practice, PET scans are commonly performed with F-18 FDG, an analogue of glucose. Malignant cells have increased glucose metabolism and therefore incorporate more glucose analogue than the surrounding normal tissues.

However, enhanced glycolytic metabolism is also seen in some benign tumors and particularly in active inflammatory processes such as infectious diseases, granulomatous lesions, and healing responses to trauma or therapy. The occurrence of high F-18 FDG uptake in these nonmalignant processes can lead to false-positive results, thus reducing the specificity of PET. However, the pattern of uptake and clinical correlation can often avoid this pitfall (11).

Furthermore, some malignant cells can have a low metabolic rate, or there may be subclinical disease (deposits of less than a few millimeters) below the resolution of the scanner leading to false-negative results.

Tracers that can detect other processes involved with malignancy, such as hypoxia and increased cell turnover, are being assessed in an attempt to improve PET scanning specificity. These are discussed later in the chapter.

One of the challenges of PET scanning has been its relative lack of structural information, except that

provided vicariously through the distribution of the radiopharmaceutical within the body related to biochemical processes that are variably expressed in different organs. This has to some degree been overcome by the development of PET scanners physically combined with CT, permitting the co-registration of the PET images with the detailed anatomic structural information acquired contemporaneously on CT or through postacquisition software co-registration with MRI (12).

Combined PET/MRI scanners are in clinical development and are likely to have an important role in HNC in the coming years (13,14).

There is an increasing motivation to perform diagnostic, contrast-enhanced CT (ceCT) as part of the PET/CT examination. By performing ceCT contemporaneously with FDG PET, it is feasible for this technology to become the primary staging tool in many high-risk HNC, providing simultaneously more accurate and convenient staging of patients (15). Acquisition of a study in radiotherapy (RT) treatment position would further increase the utility of this approach to treatment selection and planning.

Standardized Uptake Value

PET is a potentially quantitative technique. By allowing for the effects of radioactive decay, attenuation of annihilation photons by tissue, and measurement of the intrinsic scanner sensitivity, it is possible to quantify radiotracer in tissues at any given time in terms of counts/tissue mass/time. This can be subjected to secondary calculations. The most common of these is standardised uptake value (SUV), which reflects differential tracer uptake by some tissues relative to others.

Cancers typically have maximum SUV (SUV_{max}) of 2.5 or more, a threshold that has been advocated by some for differentiating benign lesions from malignancy. However, such thresholds fail to account for low apparent uptake due to partial volume effects and ignore the importance of the pattern of uptake for differentiation between benign and malignant processes.

The volume of a lesion on structural imaging does not necessarily allow accurate compensation

for partial volume effects. For example, a thin rim of viable cells in a necrotic lymph node cannot necessarily be demarcated and measured volumetrically by CT independent of the necrotic cellular elements but will be subject to partial volume effects. Technical factors including acquisition methodology and image processing and patient-related factors, including blood glucose level and body-fat content, also influence the measured SUV (16).

Although useful for confirming the visual impression of the intensity of uptake and providing a benchmark against which to compare subsequent studies, the routine use of SUV to characterize the nature of lesions is discouraged.

■ STAGING

Determining TNM stage as a summary of the extent and location of disease facilitates clinical decision making and is important for prognostication and treatment selection and planning.

Primary Tumor Staging (T-Stage)

Conventional work-up can usually provide detailed definition of the extent of primary disease and its relationship to critical anatomical planes. Although PET is highly sensitive and specific in detecting clinically evident primary disease in more than 90% to 95% of cases, its lack of independent anatomical detail limits incremental information in this setting. However, it can be helpful in better characterizing gross tumor extension of infiltrating malignancies that may be poorly assessed by anatomical imaging (2,17,18).

Occult Primary

The literature examining the role of PET for the detection of the unknown primary in patients presenting with metastatic cervical lymphadenopathy following conventional work-up presents variable results with some investigators, concluding that it is highly useful and others the opposite. The reasons for this variability are no doubt multifactorial and influenced by the

case mix of patients, degree of work-up that has led to the definition of an unknown primary scenario, the quality and era of PET imaging, and possibly the level of experience of the examining team before the staging scan (19).

Rusthoven and colleagues have published a review of the series examining the ability of PET to detect the occult primary and concluded that PET detected a primary cancer in 25% of cases, with a sensitivity, specificity, and accuracy of 88%, 75%, and 79%, respectively (20).

Although a relatively low percentage, precise localization of the primary tumor in 1 in 4 patients may help to plan more definitive therapeutic strategies. The relatively low specificity in most series probably relates to the philosophical approach of the reporting PET specialist. In this clinical setting, most such specialists will opt to read for sensitivity rather than specificity in the knowledge that no definite primary has been identified, resulting in a greater proportion of false-positive results.

The largest contemporary series published by the DAHANCA group reported the outcome of FDG PET imaging for 60 patients with squamous, undifferentiated, or adenosquamous carcinoma in neck nodes from an unknown primary site. All patients had negative physical, imaging, and panendoscopy/biopsy findings. FDG PET detected 12 (20%) head and neck primary sites as well as 6 (10%) patients with either nonhead and neck primaries or distant metastasis. FDG PET failed to detect tumor in only 3 (5%) patients for whom a primary was detected at panendoscopy subsequent to PET. False-positive PET scans were noted in 12 patients, the majority of whom had their PET scans after their biopsies. This suggested that PET had an influence on the results and that ideally the scans should be done before biopsies in this patient population (21).

One potential setting where PET may be useful is in Human Papillomavirus (HPV) positive neck disease where the likely site is the oropharynx. Greater focus can be placed in attempting to identify increased FDG avidity within the oropharynx.

An important question that remains unanswered is whether or not a negative PET can permit the omission of treatment to potential primary sites since

in most series PET negative patients have still had full mucosal irradiation with its attendant toxicity.

Nodal Staging (N-Stage)

N-stage provides important information about prognosis and guidance on the therapeutic management of neck. Occult nodal disease may be present in 20% to 30% of nodes measuring less than 1 cm on CT/MRI, in addition the physical examination can miss up to 30% to 40% of cases with nodal involvement (22).

There are multiple published series including a recent meta-analysis that have demonstrated that, for nodal staging, PET has a high positive predictive value (PPV) (>90%) and both its sensitivity and specificity are superior to conventional imaging (23). Adams and colleagues compared FDG PET with conventional imaging in the detection of nodal disease based on the histopathological

findings. FDG PET was found to have a sensitivity and specificity of 90% and 94%, respectively. This was statistically superior to CT and MRI, which were found to have a sensitivity/specificity of 82%/85% and 80%/79%, respectively (6).

Although the sensitivity of PET increases in the presence of enlarged nodes, unlike conventional imaging, it is not reliant on nodal size until the signal from malignant cells is compromised by partial volume effects. The nodal size at which this occurs is dependent on the spatial and contrast resolution of the scanner and the intensity of uptake in those cells. Nevertheless, the interpretation of FDG PET results in the neck must be tempered by the reality that its resolution for tumor less than or not equal to 5 mm remains limited (2,17).

PET detection of cervical nodal disease in a radiologic borderline left level III node shown prechemo-RT followed by a complete PET response at 12 weeks posttherapy is illustrated in Figure 10.1.

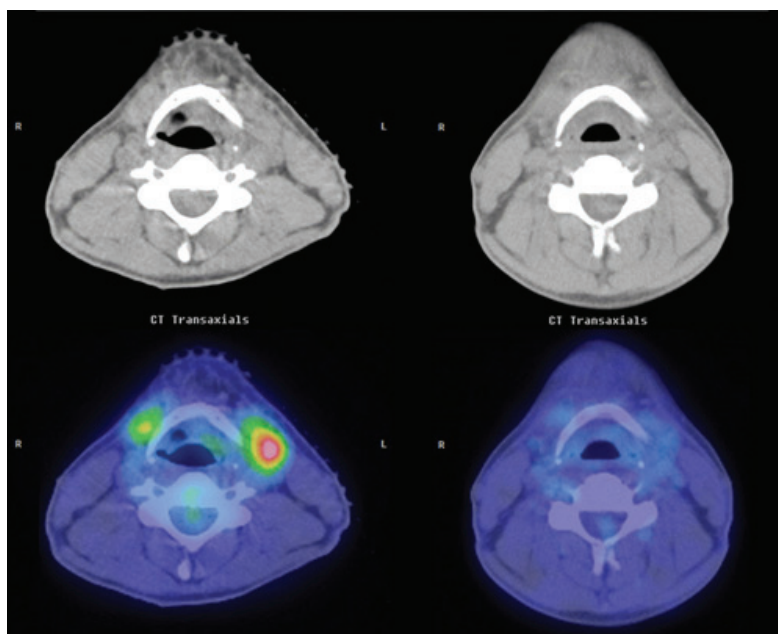


FIGURE 10.1

PET detection of cervical nodal disease in a radiologic borderline left level III node shown prechemo-RT followed by a complete PET response at 12 weeks posttherapy.

Distant Metastases Staging (M0) and Detection of Synchronous Primary Tumors

Patients with locally advanced HNSCC are at risk of having distant metastases or a synchronous second malignancy in 15% and 5% of cases, respectively. The risk of distant metastases increases with bulky or low neck disease and poorly or undifferentiated malignancy (24).

PET is potentially useful in identifying distant sites of involvement that have not been detected on routine conventional imaging and thereby prevent inappropriate radical therapy. Alternatively, it may lead to curative approaches to both tumor sites in the case of synchronous malignancies.

Published series have reported detection rates of previously unrecognized distant metastases ranging from 4% to 27% (19,20,25). This wide range of detection rates is reflective of the various patient populations studied in terms of primary site location and stage as well as the degree to which patients have been imaged with conventional methods prior to undergoing PET scanning.

Patients with no evidence of nodal involvement and small primary tumors are much less likely to harbor distant metastases, particularly if prior CT of the chest is negative.

It is reasonable to conclude that PET imaging will identify distant metastases in a variable proportion of patients prior to treatment. Even if the prevalence of such findings is less than 10%, it may nevertheless have a significant impact on treatment of individual patients and complement the advantages of superior locoregional staging.

■ MANAGEMENT

Initial Treatment

The utility of FDG PET to alter the staging following conventional imaging resulting in treatment alteration, either surgical or RT, is well recognized (8,26,27).

Koshy and colleagues reported on the impact of PET on the management of 36 patients following conventional work-up and found the TNM

staging was altered in 36% and the RT volume and dose altered in 14% and 11%, respectively (27).

In another series, FDG PET altered the TNM staging in 34%, with 10 of 35 patients upstaged and 2 of 35 downstaged. In the majority of cases, the alterations were due to a change in N-Stage (8).

Clinically Node Negative Neck (N0)

For patients presenting with an obvious primary lesion and a clinically negative neck on physical examination and CT/MRI the need to treat the primary site is obvious.

What is less obvious is whether to treat the neck with elective surgery or RT. The decision to treat the N0 neck electively, with either surgery or RT, is usually based on the perceived risk of 15% to 20% risk of occult neck disease.

In some instances, the location and extent of the primary tumor are associated with occult nodal disease often enough to mandate treatment, for example, a nasopharyngeal primary or a bulky T4 tumor at any site. On the other hand, smaller well-lateralized primary cancers may have a very low risk of failing in an untreated N0 neck.

While the PPV of FDG PET for the initial staging of nodal disease is high in patients with a clinically N+ neck and can appropriately influence treatment, the negative predictive value (NPV) for patients with a clinically N0 neck ranges between 50% and 85%. (7,28–30)

For example, Kyzas and colleagues published a meta-analysis evaluating the utility of FDG PET in the preoperative detection of cervical node metastases in HNSCC in which a subset of 10 studies incorporating 311 clinically N0 patients found a sensitivity of only 50% for PET (23).

It is worth noting that the NPV of a test is related to both its sensitivity and the prevalence of the endpoint in question. Even with a sensitivity of 50% in the N0 neck, FDG PET will have a high NPV if applied to a population of patients with superficial T1N0 oral cavity cancers simply because the rate of nodal metastasis in these cases will be less than or equal to 5%.

When the perceived risk of involvement is between 5% and 15% and the PET is negative, this may add to the confidence that the neck may be observed.

However, based on the current evidence FDG PET should not be relied upon solely to predict the avoidance of neck treatment in patients at high likelihood of nodal metastasis. If the perceived risk remains greater than 15%, then elective neck treatment should be considered even if the FDG PET is negative.

Clinically Node Positive Neck (N+)

FDG PET is not essential for most management decisions in the neck that has been determined N+ based on conventional staging, but can help to better define RT or surgical treatment fields. Based on PET scanning and superior sensitivity and specificity compared with CT and MRI, a proportion of patients (10%–30%) will have their treatment altered as a result of the detection of unanticipated nodal disease beyond those identified by conventional imaging (8). Such alterations could include the addition of more extensive neck treatment or tailoring the RT dose to address previously unrecognized nodal disease (23).

Equivocal Findings on Structural Imaging or PET

Equivocal findings detected on structural imaging, such as a 1.0 to 1.5 cm node in the neck, are not uncommon during the staging of HNC. FDG PET can be useful in determining the likelihood of malignancy on the basis that such nodes are sufficiently large to expect a signal similar to that in the primary if involved by tumor. Although reactive or inflammatory nodes may have increased FDG avidity, this is often less intense than involved nodes. An enlarged node with less intense uptake than other known sites of disease, unless clearly

necrotic on CT, is likely to be reactive. As discussed later, the use of novel radiotracers may help distinguish between inflammatory or malignant causes.

If the clinical consequences of missing disease are high, for example, missing a window of opportunity for cure, then it is best to err on the side of caution and address the suspicious lesion accordingly. Image-guided biopsy may help resolve the issue or prophylactic treatment may be indicated in some cases.

Equivocal Pulmonary Nodules

Many HNC patients have had significant tobacco and occasionally occupational dust exposure. Not infrequently, patients are found to have small (0.5–1.5 cm) pulmonary nodules on conventional imaging, the significance of which is uncertain. A meta-analysis demonstrated the PET/CT to be superior to conventional imaging for the characterization of solitary lung nodules with a sufficiently high PPV to mandate, at least, exclusion of malignancy before radical treatment of patients with FDG-avid nodules (31).

Assessment of an FDG avid pulmonary lesion needs to be made in the context of the clinical scenario. In the presence of a HNC with bulky nodal disease or low neck involvement then the lesion is more suspicious of metastatic disease, whereas if there is either no cervical nodal disease or small volume nodal disease high in the neck then it is more likely to be a primary pulmonary lesion, particularly in an older patient with a smoking history.

In HNSCC cases with non-FDG avid pulmonary nodules of 0.5 to 1.5 cm, it is not unreasonable to afford these patients the benefit of the doubt and assume the lesions are nonmalignant but lesions smaller than 0.5 cm may be too small to characterize on PET, particularly in regions of the lung that are subject to significant respiratory motion, because this leads to undersampling of the FDG signal (17).

Radiotherapy Planning

The fusing of PET images with planning CT scans to assist with RT planning has gained popularity over recent years. A number of series have assessed the utility of PET in RT planning but all have the limitation of not knowing what real impact PET fusion has had on outcome (8,26,32,33).

FDG PET fusion with planning CT does facilitate location of primary and nodal disease, but compared to planning ceCT images or fused MRI/planning ceCT images, PET appears to have a minor impact on tumor delineation for the purposes of RT target volume planning due to observed inconsistencies between PET signal and pathological correlation (34).

Post-radiotherapy Restaging

Depending on the stage and location of the tumor up to 50% of HNC patients managed initially with RT with or without systemic chemotherapy will have persistent disease, but, as a corollary of this, 50% have already been cured. In such instances the early detection of persistent disease should afford the optimal opportunity for success of salvage surgery while exclusion of disease with reasonably high certainty could avoid unnecessary further morbidity. The role of a restaging FDG PET, particularly in N+ HNSCC following curative RT, has been an area of great interest and research.

Restaging the Neck

It is not uncommon to have a residual nodal abnormality in the neck following curative RT in this group of patients. Porceddu and colleagues found that 49% of patients with N+ HNSCC had a residual nodal abnormality (≥ 1.0 cm) following RT $\pm$ systemic therapy based on structural imaging. Historically, it has been difficult to determine whether residual clinical and radiologic findings represent disease or scarring and in order not to

miss the opportunity of cure in these patients, a planned neck dissection, particularly in bulky N2 and N3 cases, has been advocated by many clinicians (35).

A number of series have demonstrated that the isolated nodal failure rate in the neck following a complete response (CR) of the primary and neck based on clinical and radiologic findings is less than 5% to 7% (1,36,37).

It has become clear therefore that patients achieving a CR in the neck, defined as no residual nodal findings greater than 1 to 1.5 cm can be observed with a very low risk of subsequent neck failure.

Some studies have shown that a restaging PET has a high NPV in the neck if the PET is performed at around 12 weeks, potentially sparing an unnecessary neck dissection (38–40). In the study by Porceddu and colleagues, 4 of 68 patients with N+ HNSCC treated with RT had a positive 12-week restaging PET scan in the neck and all had residual disease on neck dissection. At a median follow-up of 14 months, none of the patients that were observed with a PET negative scan had failed in the neck, including 30 deemed to have residual CT nodes greater than 1 cm (range 1–3.5 cm) (35).

This requires further validation in larger prospective trials, which are currently underway. One such study that is now closed to accrual after enrolling 400 patients is the PET PREVENT study conducted by the Ontario Cooperative Oncology Group. The trial was designed to assess the effectiveness of FDG PET/CT as compared to CT alone in predicting the need for neck dissection subsequent to RT plus or minus concurrent chemotherapy in HNSCC patients presenting with N2 or greater neck metastasis. Patients underwent an FDG PET/CT and ceCT before treatment and 8 to 10 weeks following the completion of treatment. The results of this important trial are pending.

Until the data from such trials are available some will still advocate a neck dissection if a residual node greater than 1.0 to 1.5 cm persists beyond 12 weeks, even if the PET is negative (38,39).

Finally, patients with residual PET avidity in the neck following RT warrant further treatment as the likelihood of residual disease will be substantially over 50% (37).

Restaging the Primary Site

The value of restaging PET to assess primary tumor response appears as effective as for the neck. Chen and colleagues found a PET accuracy of 86% for the detection of residual primary disease after treatment for oropharyngeal cancer (41). Connell and colleagues found that PET, performed around 12 weeks following RT, altered primary tumor response in 8/30 (27%) patients compared with conventional imaging alone. Six of the 8 patients with residual abnormality on CT were negative on PET and were all true negative. Two of the 8 patients had a partial response on PET and were both found to be biopsy proven false positive (8).

A meta-analysis assessing the role of PET in the follow up of HNSCC following RT or chemoradiotherapy to detect recurrent or persistent disease at either the primary site or neck reported by Isles and colleagues found that PET was highly accurate in detecting disease with a sensitivity and specificity of 94% and 82%, respectively. The PPV and NPV were 75% and 95%, respectively (42).

The Timing of Restaging PET

The timing of the posttherapy PET is critical with the optimal period appearing to be around 12 weeks. Porceddu and colleagues found that the optimal timing for the restaging PET was around 12 weeks while Yao and colleagues assessed the role of PET at a median of 15 weeks following definitive RT and found the NPV was 100% (38,39,43).

Studies have consistently shown a lower PPV, between 43% and 89% when the scan is performed too early following treatment. The probability of false-positive results diminishes with

time following treatment due to resolution of the inflammatory response and opportunity for residual tumor to resolve (8,38–41,43,44).

PET scans performed too early may also result in false negative results as this may be during a period of maximal tumor response and prior to early repopulation. Therefore, a complete metabolic response (MR) early after treatment does not necessarily indicate eradication of disease. Recently a prospective study examining the role of a restaging PET/CT performed at 8 weeks posttherapy did not find a difference in PPV or NPV compared with ceCT (45).

Greven and colleagues found a higher false-negative rate when the posttherapy PET was performed within 1 month compared with 4, 12, and 24 months following treatment. Seven of 25 (28%) patients had a recurrence following a negative PET at 1 month compared with none of 18 when the PET was negative at 4 months (44).

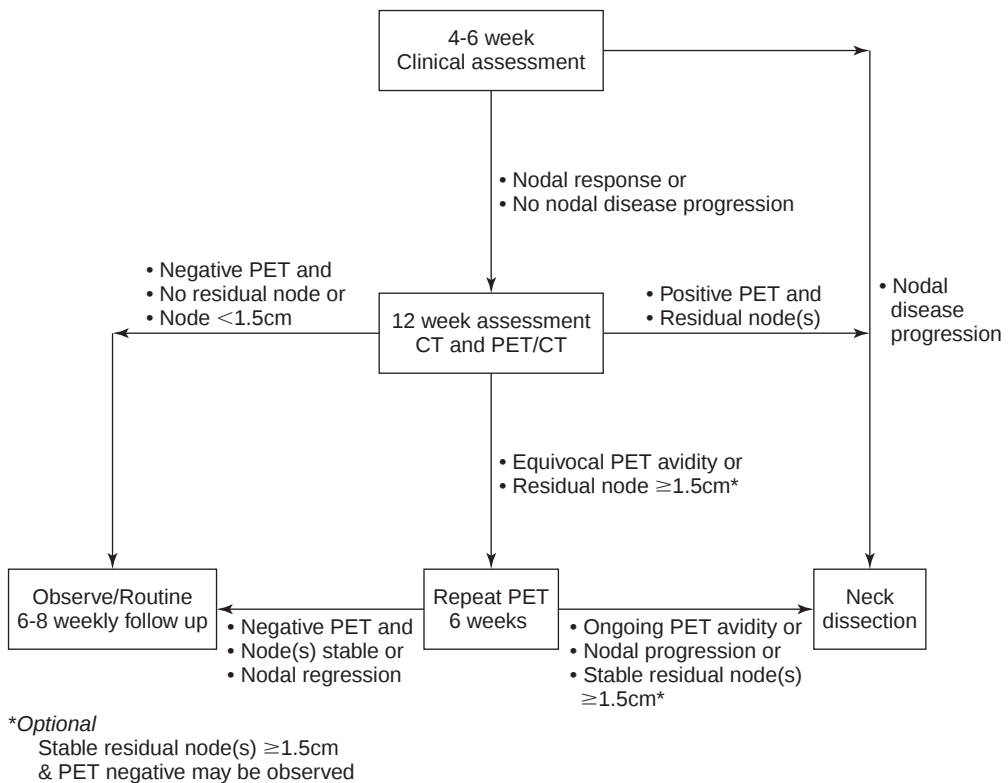
Yao and colleagues reported on 3 to 5 month posttherapy PET and found only 1 of 45 were false negative at the primary site and none of 49 in the neck (43). Porceddu and colleagues also found a high NPV if the restaging PET was performed at 12 weeks (38).

The timing of the PET around this period also means that if a neck dissection is required it can be performed prior to the establishment of late radiation fibrosis.

PET guided management of the neck in patients who achieve a CR at the primary site is described in Figure 10.2.

■ THERAPEUTIC MONITORING AND PROGNOSIS

FDG PET has been investigated as a prognostic tool for the independent prediction of treatment outcome in HNC. As such, attempts have been made to correlate aspects of PET results obtained before, during and following RT with eventual tumor control. If demonstrated and validated this potential prognostic capability could lead to beneficial

**FIGURE 10.2**

PET-guided management of the neck following radiation therapy and CR at the primary site.

individualization of treatment approaches for patients based, in part, on the results of their PET scans.

A number of investigators have examined the correlation of thresholds of maximum SUV, and MR, with outcome (46–48).

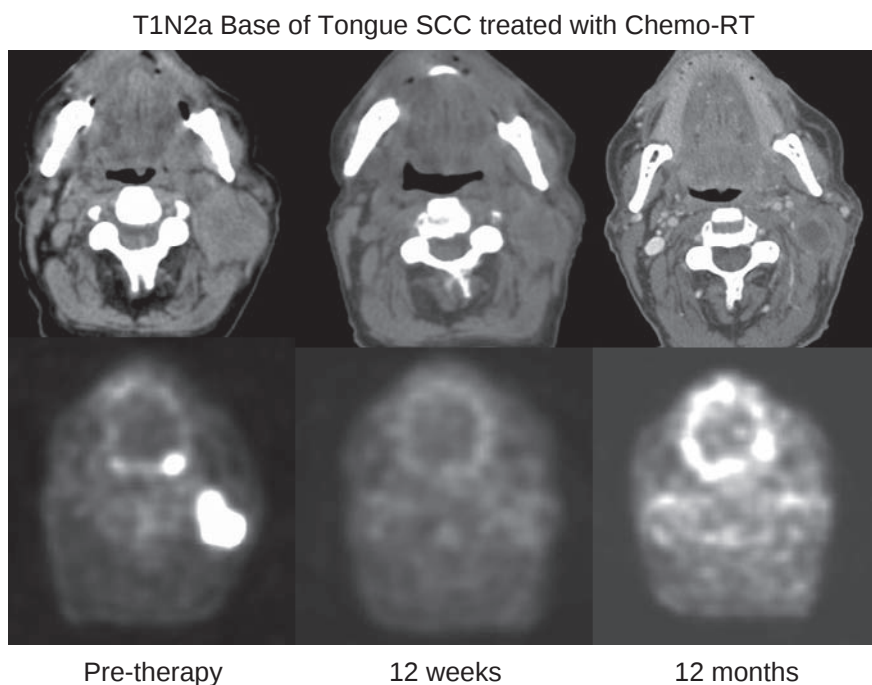
Brun and colleagues evaluated the MR in 47 patients with HNSCC. Patients underwent a pretreatment PET (PET_1) followed by another PET_2 1 to 3 weeks following the commencement of radical RT with evaluation of MR. Low and high MR FDG PET, with median value as cut-off, was associated with CR in 96% and 62% ($P = .007$), respectively. A significant difference was also seen with local control, 96% versus 55% ($P = .002$)

and 5 year survival, 72% versus 35% ($P = .0042$), respectively (9). These data suggest that tumors with low FDG-avidity may be more resistant to current therapies.

Irrespective of baseline FDG uptake, Connell and colleagues found a significant difference in disease free survival and overall survival favoring those with a complete MR on PET/CT at 12 weeks (8).

A recent summary of published data found that a complete MR has a high NPV. This would be anticipated to extrapolate into a favorable prognosis (49).

Thus, FDG PET as a prognostication tool appears promising but how this information will be used clinically requires further evaluation.

**FIGURE 10.3**

PET response predicting nodal outcome following curative radiotherapy ahead of structural imaging.

PET response predicting nodal outcome following curative RT ahead of structural imaging is illustrated in Figure 10.3.

■ SURVEILLANCE AND RESTAGING FOR RECURRENCE HNSCC

The 5-year rate of locoregional recurrence, second primary, and development of distant metastases are 40% to 50%, 10% to 30%, and 15% to 20%, respectively. While there are no curative options for patients with distant metastases, early detection of a new primary or early localized recurrence provides a greater possibility of cure (4).

One study demonstrated patients with early recurrent disease who underwent salvage

surgery had a 70% 2-year relapse free survival compared with 22% in patients with advanced recurrence (4).

Confirming suspected relapse following RT can be difficult because of the resulting anatomic changes due to inflammation, edema, and/or fibrosis hindering the interpretation of the physical examination and radiologic findings. Biopsy is helpful if positive but uncertainty remains if negative due to the potential for sampling error. Serial CT or MRI scanning may also help, but this relies on tumor progression over a period of time and may miss the opportunity for salvage.

Kim and colleagues reported on a study aimed at evaluating the ability of FDG PET/CT to detect second primary cancers and distant metastases in patients with a previous history of a HNC. Of the 349 patients, 14 (4%) were found to

have a second primary cancer and 7% had distant metastases with a mean follow-up of 15 months following treatment. The sensitivity and specificity of PET were 97.5% and 92.6%, respectively, and the PPV and NPV were 62.9% and 99.7%, respectively (50).

PET scanning is costly and therefore the optimal frequency and cost-effectiveness of PET/CT surveillance following treatment of HNSCC require further evaluation.

Nasopharyngeal Carcinoma (NPC)

The primary treatment for NPC is RT with or without concurrent chemotherapy depending on stage. Despite recent improvements in patient outcomes as a result of the addition of chemotherapy and the utilization of more conformal RT techniques, such as IMRT, about 25% of patients will develop recurrent disease.

In the majority of cases, this is due to distant metastasis. However, some will fail at the primary site or in neck nodes. Detecting early locoregional recurrence is important as selected patient can be salvaged with surgery or RT with or without systemic therapy. Noninvasive diagnostic techniques such as CT and MRI are important tools in aiding in the diagnosis of recurrence but distinguishing late RT effects, such as edema and fibrosis from recurrent tumor, can be challenging. The fact that some recurrences are submucosal or deep-seated can make detection by fiberoptic inspection difficult. Blind biopsies of the previously irradiated nasopharynx, which often remains thickened, may be subject to sampling error or complicated by mucosal ulceration. Because of these challenges, PET scanning has been investigated as a tool for detecting recurrence.

Liu and colleagues performed a systematic review to compare FDG-PET, CT, and MRI imaging for the diagnosis of local residual or recurrent NPC. The authors found the pooled sensitivity estimates for PET (95%) were significantly higher than CT (76%) ($P < .001$) and MRI (78%) ($P < .001$). The

pooled specificity estimates for PET (90%) were significantly higher than CT (59%) ($P < .001$) and MRI (76%) ($P < .001$).

The authors concluded that FDG-PET was the best modality for the diagnosis of local residual or recurrent NPC (51).

Detection of recurrence by monitoring serum Epstein Barr Virus (EBV) levels is gaining popularity. The degree to which PET will be complementary to this form of monitoring remains to be determined. It may be that rising EBV titers would prompt PET scanning in order to identify the location of the recurrence.

Utility of PET in the restaging of NPC following chemo-RT demonstrating no PET avidity in a radiologic residual abnormality in the nasopharynx is illustrated in Figure 10.4.

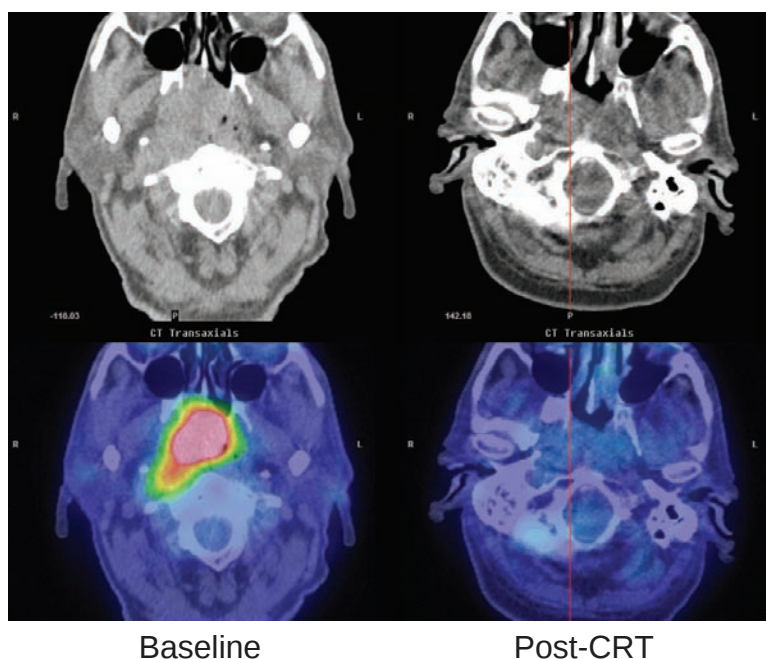
■ COST EFFECTIVENESS

There have been some significant advances in recent years in PET scanning that have enhanced image quality. These include improved detector design, electronics, and iterative reconstruction methods.

Given PET has shown to be superior to conventional imaging with respect to sensitivity and specificity a case can be made to go directly to PET/ceCT for the staging and restaging of HNSCC (52).

Although FDG PET/CT has been more expensive than conventional imaging, enhanced throughput leads to less cost per PET scan ratio through more efficient use of isotope and staff and better amortization of equipment costs. The ability of PET to prevent expensive additional tests or avoid futile treatments especially through detection of distant disease unrecognized by conventional work-up, can increase the potential cost effectiveness.

There are relatively few formal studies that have addressed the cost-effectiveness of this modality in HNC and is dependent on a number of factors such as the health economics of the region and patient throughput. At this stage, the

**FIGURE 10.4**

Utility of PET in the restaging of NPC following chemo-RT demonstrating no PET avidity in a radiologic residual abnormality in the nasopharynx.

cost-effectiveness of proceeding straight to a PET/CT remains under investigation (53).

■ BIOLOGICAL CHARACTERIZATION WITH PET

Current Limitations in HNSCC Management

The management of HNSCC is predominantly based on TNM staging and pathologic findings. Transformation from normal to malignant cells is due to a series of acquired genetic and molecular changes leading to tumor formation (54). As a result, tumors tend to be biologically heterogeneous, and therefore for the same pathologic findings and TNM staging tumors may have differing outcomes despite the same treatment.

Further intensification with chemotherapy and RT strategies are unlikely to yield any substantial

improvements in outcome as current treatments are at the limits of normal tissue tolerance. Tumor characterization beyond TNM and histologic subclassification is required to advance our understanding of this disease. Such characterization represents the cutting edge of contemporary cancer research and is beginning to have a therapeutic impact.

Targeted therapies aimed at known genetic/molecular aberrations or their downstream products provide potential alternatives to improving outcome without the added toxicity from current treatments (55).

Two important biomarkers have emerged in the management of HNSCC, the epidermal growth factor receptor (EGFR), which is usually over-expressed in HNSCC, and HPV tumor status. Both of these have implications in treatment and outcome (56).

The use of novel markers combined with PET can extend its role beyond that of simply a tool for

anatomic tumor delineation to one of biologically characterizing tumors at diagnosis, during and posttherapy. Potential advantages of characterizing tumors with PET include the fact it provides non-invasive and *in vivo* assessment of tumor function. As such, it can be done repeatedly throughout the course of the treatment package.

Novel Radiotracers

Radiotracers allow assessment of various processes such as cell proliferation, protein synthesis, cell membrane production, hypoxia, and bone turnover. In addition, the ability to image receptors such as EGFR is emerging. It is beyond the scope of this chapter to discuss each tracer in detail. Kumar and colleagues have published a comprehensive review summarizing many of the novel tracers (57).

Due to the general availability and favorable physical properties of F-18 (relative long half-life and low positron range), much effort has been directed to fluorinated compounds. ^{11}C -Thymidine has shown promise but C-11 compounds are not very practical for routine clinical application with production yields seldom being adequate for more than a few patient studies (58).

A summary of selected fluorinated tracers of possible utility in characterizing abnormalities related to HNC are summarized in Table 10.1.

Clinical Applications

Hypoxic imaging

Hypoxia has long been recognized as an adverse determinant of RT treatment outcome in HNC (59). Functional imaging to detect hypoxia offers the advantage of being less invasive and more practical than polarographic probes. New approaches to overcome hypoxia such as the concurrent use of the hypoxic cytotoxin tirapazamine have been evaluated (11).

Fluoromisonidazole (FMISO) has been the most extensively studied agent in both animals and humans (10,60,61).

TABLE 10.1

Summary of selected fluorinated tracers of possible utility in characterizing abnormalities related to HNC

Radiopharmaceutical	Mechanism of action
^{18}F -fluoro-2-deoxy-D-glucose (FDG)	Glucose uptake
^{18}F -Fluoromisonidazole (FMISO)	Detection of hypoxia
^{18}F -fluoroazamycin arabinoside (FAZA)	Detection of hypoxia
^{18}F -fluorothymidine (FLT)	Cell proliferation
^{18}F -fluoroethyltyrosine (FET)	Protein synthesis
^{18}F -fluorocholine (FCH)	Cell membrane production
^{18}F -fluoride	Bone turnover

Rischin and colleagues have reported on the ability of F-18 FMISO PET to stratify prognosis in patients receiving conventional RT and tirapazamine (10,62).

Fluoromisonidazole is relatively lipophilic, which leads to reduced resolution between hypoxic and normal tissue. Fluorine-18 fluoro-azamycin arabinoside (FAZA) appears to have more favorable imaging properties through its more rapid soft tissue clearance leading to improved hypoxic/normal tissue definition (63).

Illustration of a FAZA PET scan demonstrating uptake in a hypoxic node is shown in Figure 10.5.

A number of studies have recently been published examining the role of targeted therapies in the management of HNSCC. There are now agents directed at a number of cellular targets and processes. One such agent is Sunitinib directed at the vascular-endothelial growth factor receptor which is involved in angiogenesis. These therapies could increase tumor hypoxia by reducing vascularity or reduce it by improving the efficiency of oxygen delivery to the tumor by way of "vascular normalization" (64, 65).

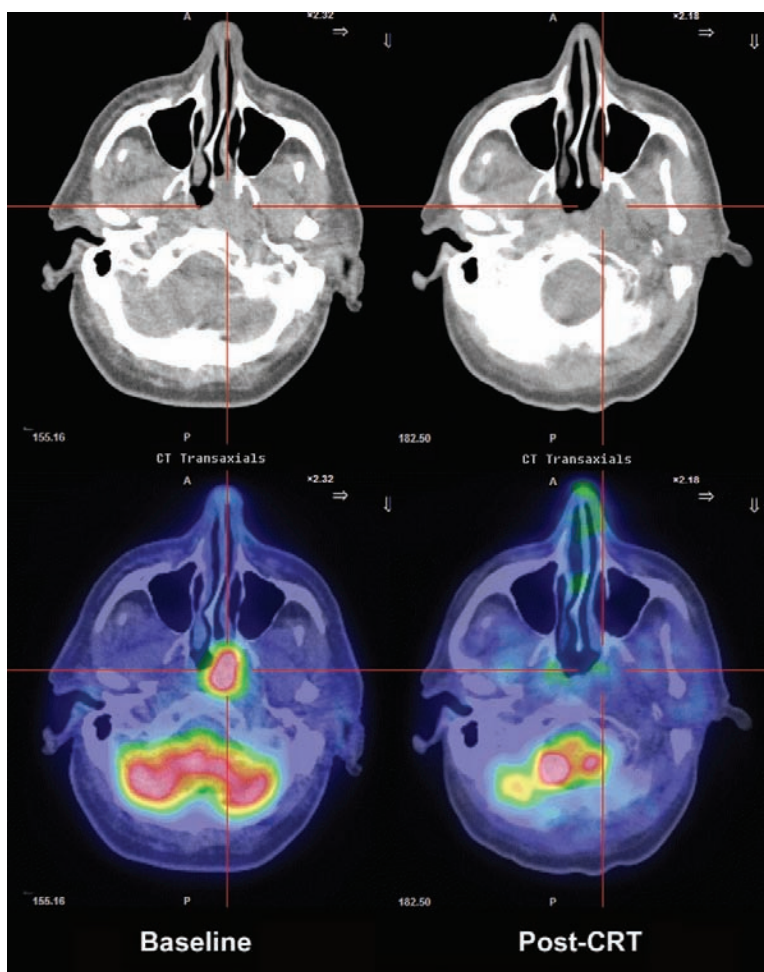
**FIGURE 10.5**

Illustration of a FAZA PET scan demonstrating uptake in a hypoxic node.

The ability of hypoxia imaging with PET to demonstrate changes in hypoxia during treatment with these agents has been demonstrated in preclinical models of SCC and offers promise for their evaluation in clinical practice (54).

Proliferation imaging

Fluorine-18 fluorothymidine (FLT) is a thymidine analogue and its uptake is closely correlated with cellular proliferation and the proliferation marker Ki-67. The complementary use of FLT PET with FDG PET may increase the specificity

of functional imaging by distinguishing between inflammatory and malignant processes, such as a solitary pulmonary nodule, and aid in assessing early therapeutic response (66, 67).

However, it must be noted that germinal centers in reactive lymph nodes have active cellular proliferation and can be positive on FLT PET. Therefore, the utility of this scanning technique may be limited to characterization of nonnodal recurrences.

The role of FLT PET in clinical practice is still to be defined and there are a number of clinical trials assessing its role in the evaluation of treatment

planning and tumor response in HNSCC (www.clinicaltrials.gov).

Some malignancies have a low proliferation rate, such as low-grade adenocarcinomas, which can result in false negative findings with FDG PET. These tumors have high choline content, which is used in cell membrane production. Radiolabeled choline analogues are also being evaluated as potential PET traces (68).

PET Detection of EGFR

EGFR is a transmembrane protein with tyrosine kinase (TK) activity that on activation results in a cascade of events leading to cell proliferation. Inhibition of the receptor with the monoclonal antibody cetuximab coupled with RT in the curative management of locally advanced HNSCC results in superior locoregional control and overall survival compared with RT alone (56).

Although the presence of EGFR is associated with worse prognosis, there is no established correlation between EGFR expression and treatment response.

There is preclinical data using mouse models demonstrating that PET can be used to detect EGFR, *in vivo*. This has the potential predictive role in optimizing patient selection for an EGFR inhibitor or monitoring response to therapy.

Two major strategies for visualizing EGFR have been studied: labeling small molecules such as TK inhibitors and labeling monoclonal antibodies. In a review article, Pantaleo and colleagues describe some of the ongoing research that has been done in this field (69).

Cai and coworkers combined cetuximab with ^{64}Cu to form a PET probe known as ^{64}Cu -DOTA-cetuximab. This has been tested with small animal PET in 7 xenograft mouse models and demonstrated that the probe was taken up higher in those xenografts with greater expression of EGFR (70).

Zr-89, a radionuclide with a physical half-life of around 3 days, has been used to label and track various antibodies that may be of relevance to the

treatment of HNSCC, including cetuximab (71). Currently there is a lack of specificity with these probes, as many normal tissues express EGFR and therefore further work is required in this area.

■ CONCLUSION

FDG PET is a functional diagnostic tool used in the anatomic delineation of cancer by detecting increased glucose metabolism of tumor cells compared with surrounding normal tissues. It is currently complementary to conventional structural imaging in the staging of HNSCC because of its superior contrast between normal and malignant disease, leading to high sensitivity/specificity and predictive values, as demonstrated by a number of nonrandomized studies and a meta-analysis.

Whether this should be the first imaging investigation of choice, especially with the development of PET/ceCT remains controversial. There is no doubt FDG PET can provide additional information to the conventional work-up. However the proportion of patients for which it does so ranges from 10% to 30%. It is likely that the judicious use of PET in selected clinical scenarios will maximize its benefit. Such scenarios are expected to include posttreatment assessment of the neck and primary site, particularly in the presence of residual abnormalities, and possibly in the detection of the unknown primary site.

Although there does appear to be merit in long-term surveillance with PET in the detection of recurrence or second primary, the frequency of scanning and the cost-effectiveness of this approach remains unknown.

While fusion of PET with RT planning scans has gained popularity, and does confirm extent of disease, its usefulness in tumor delineation remains to be defined as more rigorous methodologies are developed and strategies to assess the accuracy of planning are refined.

In the era of "Personalized treatment" and targeted agents, novel radiotracers may allow for tumor biological characterization allowing for tailoring of therapy and potentially assistance in therapeutic monitoring.

■ REFERENCES

- Pellitteri PK, Ferlito A, Rinaldo A, et al. Planned neck dissection following chemoradiotherapy for advanced head and neck cancer: is it necessary for all? *Head Neck*. 2006;28(2):166–175.
- Ahn PH, Garg MK. Positron emission tomography/computed tomography for target delineation in head and neck cancers. *Sem Nucl Med*. 2008;38(2):141–148.
- Vernon MR, Maheshwari M, Schultz CJ, et al. Clinical outcomes of patients receiving integrated PET/CT-guided radiotherapy for head and neck carcinoma. *Int J Radiat Oncol Biol Phys*. 2008;70(3):678–684.
- Vermeersch H, Loose D, Ham H, et al. Nuclear medicine imaging for the assessment of primary and recurrent head and neck carcinoma using routinely available tracers. *Eur J Nucl Med Mol Imaging*. 2003;30(12):1689–1700.
- Jeong H, Baek C, Son Y, et al. Use of integrated 18F-FDG PET/CT to improve the accuracy of initial cervical nodal evaluation in patients with Head and neck squamous cell carcinoma. *Head Neck*. 2007;29(3):203–210.
- Adams S, Baum RP, Stuckensen T, et al. Prospective comparison of 18F-FDG PET with conventional imaging modalities (CT, MRI, US) in lymph node staging of head and neck cancer. *Eur J Nucl Med*. 1998;25(9):1255–1260.
- Schoder H, Carlson DL, Kraus DH, et al. 18F-FDG PET/CT for detecting nodal metastases in patients with oral cancer staged N0 by clinical examination and CT/MRI. *J Nucl Med*. 2006;47:755–762.
- Connell CA, Corry J, Milner AD, et al. Clinical impact of, and prognostic stratification by, F-18 FDG PET/CT in head and neck mucosal squamous cell carcinoma. *Head Neck*. 2007;29(11):986–995.
- Brun E, Kjellén E, Tennvall J, et al. FDG PET studies during treatment: prediction of therapy outcome in head and neck squamous cell carcinoma. *Head Neck*. 2002;24(2):127–135.
- Rischin D, Hicks RJ, Fisher R, et al. Prognostic significance of [18f]-misonidazole positron emission tomography-detected tumor hypoxia in patients with advanced head and neck cancer randomly assigned to chemoradiation with or without tirapazamine: a sub-study of Trans-Tasman Radiation Oncology Group Study 98.02. *J Clin Oncol*. 2006; 24:2098–2104.
- Wang G, Lau EW, Shakher R, et al. How do oncologists deal with incidental abnormalities on whole-body fluorine-18 fluorodeoxyglucose PET/CT? *Cancer*. 2007;109:117–124.
- Schöder H, Yeung HW, Gonen M, et al. Head and neck cancer: clinical usefulness and accuracy of PET/CT image fusion. *Radiology*. 2004;231:65–72.
- Delso G, Ziegler S. PET/MRI system design. *Eur J Nucl Med Mol Imaging*. 2009;36(suppl 1):S86–S92.
- Hicks RJ, Lau EW. PET/MRI: a different spin from under the rim. *Eur J Nucl Med Mol Imaging*. 2009;36:(suppl 1):S10–S14.
- Hicks RJ, Ware RE, Lau EW. PET/CT: will it change the way that we use CT in cancer imaging? *Cancer Imaging*. 2006;6:S52–S62.
- Visvikis D, Costa DC, Croasdale I, et al. CT-based attenuation correction in the calculation of semi-quantitative indices of [18F]FDG uptake in PET. *Eur J Nucl Med Mol Imaging*. 2003;30:344–353.
- McGuirt WF, Greven K, Williams D III, et al. PET scanning in head and neck oncology: a review. *Head Neck*. 1998;20(3):208–215.
- Laubenbacher C, Saumweber D, Wagner-Manslau C, et al. Comparison of fluorine-18-fluorodeoxyglucose PET, MRI and endoscopy for staging head and neck squamous-cell carcinomas. *J Nucl Med*. 1995; 36(10): 1747–1757.
- Fogarty GB, Peters LJ, Stewart J, et al. The usefulness of fluorine 18-labelled deoxyglucose positron emission tomography in the investigation of patients with cervical lymphadenopathy from an unknown primary tumor. *Head Neck*. 2003;25(2):138–145.
- Rusthoven KE, Koshy M, Paulino AC, et al. The role of fluorodeoxyglucose positron emission tomography in cervical lymph node metastases from an unknown primary tumor. *Cancer*. 2004;101(11):2641–2649.
- Johansen J, Buus S, Loft A, et al. Prospective study of 18FDG-PET in the detection and management of patients with lymph node metastases to the neck from an unknown primary tumor. Results from the DAHANCA-13 study. *Head Neck*. 2008;30(4): 471–478.
- Whitehurst JO, Droulias CA. Surgical treatment of squamous cell carcinoma of the oral tongue: factors influencing survival. *Arch Otolaryngol*. 1977;103(4): 212–215.
- Kyzas PA, Evangelou E, Denaxa-Kyza D, et al. ¹⁸F-Fluorodeoxyglucose positron emission tomography to evaluate cervical node metastases in patients with head and neck squamous cell carcinoma: a meta-analysis. *J Natl Cancer Inst*. 2008;100:712–720.
- Erkal HS, Mendenhall WM, Amdur RJ, et al. Synchronous and metachronous squamous cell carcinomas of the head and neck mucosal sites. *J Clin Oncol*. 2001;19:1358–1362.
- Goerres GW, Schmid DT, Grätz KW, et al. Impact of whole body positron emission tomography on initial staging and therapy in patients with squamous cell carcinoma of the oral cavity. *Oral Oncol*. 2003; 39(6):547–551.
- Koshy M, Paulino AC, Howell R, et al. F-18FDGPET-CT fusion in radiotherapy treatment planning for head and neck cancer. *Head Neck*. 2005;27(6):494–502.

27. Agarwal V, Branstetter BF IV, Johnson JT. Indications for PET/CT in the Head and Neck. *Otolaryngol Clin North Am.* 2008;41(1):23–49.
28. Layland MK, Sessions DG, Lenox J, et al. The influence of lymph node metastasis in the treatment of squamous cell carcinoma of the oral cavity, oropharynx, larynx and hypopharynx: N0 versus N+. *Laryngoscope.* 2005; 115(4):629–639.
29. Stoeckli SJ, Steinert H, Pfaltz M, et al. Is there a role for positron emission tomography with 18F-fluorodeoxyglucose in the initial staging of nodal negative oral and oropharyngeal squamous cell carcinoma. *Head Neck.* 2002; 24:345–349.
30. Ng SH, Yen TC, Chang JT, et al. Prospective study of [18F]fluorodeoxyglucose positron emission tomography and computed tomography and magnetic resonance imaging in oral cavity squamous cell carcinoma with palpably negative neck. *J Clin Oncol.* 2006; 24(27):4371–4376.
31. Cronin P, Dwamena B, Kelly A, Carlos R. Solitary pulmonary nodules: meta-analytic comparison of cross-sectional imaging modalities for diagnosis of malignancy. *Radiology.* 2008;246(3):772–782.
32. Ha PK, Hdeib A, Goldenberg D, et al. The role of positron emission tomography and computed tomography fusion in the management of early-stage and advanced-stage primary head and neck squamous cell carcinoma. *Arch Otolaryngol Head Neck Surg.* 2006;132(1):12–16.
33. Daisne J, Duprez T, Weynant B, et al. Impact of image coregistration with computed tomography (CT), magnetic resonance (MR) and positron emission tomography with fluorodeoxyglucose (FDG-PET) on delineation of GTV's in oropharyngeal, laryngeal and hypopharyngeal tumors. *Int J Radiat Oncol Biol Phys.* 2002;54s:15–16.
34. Guido A, Fuccio L, Rombi B, et al. Combined 18F-FDG-PET/CT imaging in radiotherapy target delineation for head-and-neck cancer. *Int J Radiat Oncol Biol Phys.* 2009;73(3):759–763.
35. Porceddu SV, Pryor DI, Doughton J, et al. Results of a prospective PET-guided management of the neck study in node positive head and neck squamous cell carcinoma (HNSCC) following curative radiotherapy with or without concurrent chemotherapy. *Oral Oncology.* 2009;3(1):s64.
36. Porceddu SV, Sidhom M, Foote M, et al. Predicting regional control based on pre-treatment nodal size in squamous cell carcinoma of the head and neck treated with chemo-radiotherapy: a clinician's guide. *J Med Imaging and Radiat Oncol.* 2008;52(5):491–496.
37. Corry J, Peters L, Fisher R, et al. N2-N3 neck nodal control without planned neck dissection for clinical/radiologic complete responders—Results of Trans Tasman Radiation Oncology Group Study 98.02. *Head Neck.* 2008;30(6):737–742.
38. Porceddu SV, Jarmolowski E, Hicks RJ, et al. Utility of positron emission tomography for the detection of disease in residual neck nodes after (chemo) radiotherapy in head and neck cancer. *Head Neck.* 2005;27(3):175–181.
39. Yao M, Smith RB, Graham MM, et al. The role of FDG PET in management of neck metastasis from head-and-neck cancer after definitive radiation treatment. *Int J Radiat Oncol Biol Phys.* 2005;63(4):991–999.
40. Ware RE, Matthews JP, Hicks RJ, et al. Usefulness of fluorine-18 fluorodeoxyglucose positron emission tomography in patients with a residual structural abnormality following definitive treatment for squamous cell carcinoma of the head and neck. *Head Neck.* 2004;26:1008–1017.
41. Chen AY, Vilaseca I, Hudgins PA, et al. PET-CT vs contrast-enhanced CT: what is the role for each after chemoradiation for advanced oropharyngeal cancer? *Head Neck.* 2006;28(6):487–495.
42. Isles MG, McConkey C, Mehanna HM. A systematic review and meta-analysis of the role of positron emission tomography in the follow up of head and neck squamous cell carcinoma following radiotherapy or chemoradiotherapy [review]. *Clin Otolaryngol.* 2008;33(3):210–222.
43. Greven KM, Williams DW III, McGuirt WF Sr, et al. Serial positron emission tomography scans following radiation therapy of patients with head and neck cancer. *Head Neck.* 2001;23:942–946.
44. Yao M, Graham MM, Smith RB, et al. Value of FDG PET in assessment of treatment response and surveillance in head-and-neck cancer patients after intensity modulated radiation treatment: a preliminary report. *Int J Radiat Oncol Biol Phys.* 2004;60:1410–1418.
45. Moeller BJ, Rana V, Cannon BA, et al. Prospective risk-adjusted [18F]Fluorodeoxyglucose positron emission tomography and computed tomography assessment of radiation response in head and neck cancer. *J Clin Oncol.* 2009;27(15):2509–2515.
46. Allal AS, Dulguerov P, Allaoua M, et al. Standardized uptake value of 2-[(18F)] fluoro-2-deoxy-D-glucose in predicting outcome in head and neck carcinomas treated by radiotherapy with or without chemotherapy. *J Clin Oncol.* 2002;20(5):1398–1404.
47. Machtay M, Narwa M, Andrej J, et al. Pretreatment FDG-PET standardized uptake value as a prognostic factor for outcome in head and neck cancer. *Head Neck.* 2009;31(2):195–201.
48. Suzuki H, Hasegawa Y, Terada A, et al. FDG-PET predicts survival and distant metastasis in oral

- squamous cell carcinoma. *Oral Oncol.* 2009;45(7):569–573.
49. Schöder H, Fury M, Lee N, Kraus D. PET monitoring of therapy response in head and neck squamous cell carcinoma. *J Nucl Med.* 2009;50(suppl 1):74S–88S.
 50. Kim SY, Roh JL, Yeo NK, et al. Combined 18F-fluorodeoxyglucose-positron emission tomography and computed tomography as a primary screening method for detecting second primary cancers and distant metastases in patients with head and neck cancer. *Ann Oncol.* 2007;18(10):1698–1703.
 51. Liu T, Xu W, Yan WL, et al. FDG-PET, CT, MRI for diagnosis of local residual or recurrent nasopharyngeal carcinoma, which one is the best? A systematic review. *Radiother Oncol.* 2007;85(3):327–335.
 52. Valk PE, Pounds TR, Tesar RD, Hopkins DM, Haseman MK. Cost-effectiveness of PET imaging in clinical oncology. *Nucl Med Biol.* 1996;23:737–743.
 53. Hollenbeak CS, Lowe VJ, Stack BC Jr. The cost-effectiveness of fluorodeoxyglucose 18-F positron emission tomography in the N0 neck. *Cancer.* 2001;92(9):2341–2348.
 54. Haddad RI, Shin DM. Recent advances in head and neck cancer. *N Engl J Med.* 2008;359:1143–1154.
 55. Lorch JH, Posner MR, Wirth LJ, Haddad RI. Seeking alternative biological therapies: the future of targeted molecular treatment. *Oral Oncol.* 2009;45(4–5):447–453.
 56. Bonner JA, Harari PM, Giralt J, et al: Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med.* 2006;4:567–578.
 57. Kumar R, Dhanpathi H, Basu S, Rubello D, Fanti S, Alavi A. Oncologic PET tracers beyond [(18)F]FDG and the novel quantitative approaches in PET imaging [review]. *J Nucl Med Mol Imaging.* 2008;52(1):50–65.
 58. Hicks RJ. Beyond FDG: novel PET tracers for cancer imaging. *Cancer Imaging.* 2003;4:22–24.
 59. Brizel DM, Sibley GS, Prosnitz LR, et al. Tumor hypoxia adversely affects the prognosis of carcinoma of the head and neck. *Int J Radiat Oncol Biol Phys.* 1997;38:285–289.
 60. Lee ST, Scott AM. Hypoxia positron emission tomography imaging with 18F-fluoromisonidazole. *Semin Nucl Med.* 2007;37:451–461.
 61. Hicks RJ, Rischin D, Fisher R, et al. Utility of FMISO PET in advanced head and neck cancer treated with chemoradiation incorporating a hypoxia-targeting chemotherapy agent. *Eur J Nucl Med Mol Imaging.* 2005;32:1384–1391.
 62. Thorwarth D, Eschmann SM, Scheiderbauer J, Paulsen F, Alber M. Kinetic analysis of dynamic 18F-fluoromisonidazole PET correlates with radiation treatment outcome in head-and-neck cancer. *BMC Cancer.* 2005;5:152.
 63. Hicks RJ, Dorow D, Roselt P. PET tracer development—a tale of mice and men. *Cancer Imaging.* 2006;6:s102–s106.
 64. Jain RK. Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. *Science.* 2005;307:58–62.
 65. Solomon B, Binns D, Roselt P, et al. Modulation of intratumoral hypoxia by the epidermal growth factor receptor inhibitor gefitinib detected using small animal PET imaging. *Mol Cancer Ther.* 2005;4: 1417–1422.
 66. Vesselle H, Grierson J, Muzi M, et al. In vivo validation of 3′-deoxy-3′-[(18)F]fluorothymidine ([18F]FLT) as a proliferation imaging tracer in humans: correlation of [18F]FLT uptake by positron emission tomography with Ki-67 immunohistochemistry and flow cytometry in human lung tumors. *Clin Cancer Res.* 2002; 8:3315–3323.
 67. Buck AK, Halter G, Schirrmeister H, et al. Imaging proliferation in lung tumors with PET: 18F-FLT versus 18F-FDG. *J Nucl Med.* 2003;44:1426–1431.
 68. DeGrado T, Baldwin S, Wang S, et al. Synthesis and evaluation of 18F-labeled choline analogs as oncologic PET tracers. *J Nucl Med.* 2001;42:1805–1814.
 69. Pantaleo MA, Nannini M, Maleddu A, et al. Experimental results and related clinical implications of PET detection of epidermal growth factor receptor(EGFR) in cancer. *Annals of Oncology.* 2009;20:213–226.
 70. Cai W, Chen K, He L, et al. Quantitative PET of EGFR expression in xenograftbearing mice using 64Cu-labeled cetuximab, a chimeric anti-EGFR monoclonal antibody. *J Nucl Med Mol.* 2007;34: 850–858.
 71. Perk LR, Visser GW, Vosjan MJ, et al. (89)Zr as a PET surrogate radioisotope for scouting biodistribution of the therapeutic radiometals (90)Y and (177) Lu in tumor-bearing nude mice after coupling to the internalizing antibody cetuximab. *J Nucl Med.* 2005;46(11):1898–1906.

CHAPTER 11

Diagnostic and Therapeutic Advances in Multidisciplinary Care for Nasopharyngeal Cancer

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■ INTRODUCTION

Nasopharyngeal carcinoma (NPC) is an unique malignancy with distinctive histological and epidemiological features that are different from other epithelial cancers of the head and neck region. Firstly, the Epstein-Barr virus (EBV) genome is present in more than 80% of NPC cases worldwide, and in nearly 100% of NPC cases in the endemic regions. Secondly, NPC is an endemic in certain geographic regions such as in Southeast Asia, where the peak incidence rate is up to 20 to 30 per 100,000 person-years, which is more than 20 times higher than that in Caucasian countries. The major curative treatment modality for NPC includes radiation therapy (RT) and chemotherapy. Modern RT technique with or without chemotherapy reduces local failures to less than 15%, but unfortunately this is still associated with a significant distant failure rate of 20% to 30% (1). Recent advances in diagnostic imaging has helped to improve accuracy in diagnosis, treatment, and therapeutic monitoring. On the other hand, the rapid growth of basic science has increased our understanding on the molecular biology of NPC, which holds the key to finding more specific targets for therapeutic intervention. This chapter

aims to discuss the development of NPC treatment, with special focus on the major diagnostic and therapeutic advances in the multidisciplinary treatment of this disease.

■ INCREASING UNDERSTANDING OF MOLECULAR PATHOGENESIS

The course of NPC pathogenesis involves cumulative genetic and epigenetic events. Genome-wide microarray analysis has unravelled multiple genetic alterations, which involve amplification or gain-of-function mutations of specific oncogenes, and deletion or mutation of specific tumor suppressor genes. Epigenetic studies have revealed that many tumor suppressor genes are silenced by hypermethylation of their promoters at the CpG islands (2,3). Endemic NPC is universally associated with clonal expansion of EBV genomes (4). Some of these EBV genes confer host cell “immortalization.” For instance, the latent membrane protein 1 (LMP-1), plays an important role in amplification or overexpression of epidermal growth factor receptor (EGFR), which in turn deregulates a cascade of downstream signaling transduction (5–8). However, unlike the full genomic expression of

other lymphoproliferative disorders, only a small proportion of these EBV antigens are expressed in NPC. Silencing of the other EBV immunodominant genes by CpG methylation is thought to be the cause of latent infection enabling the NPC cells to evade the host's immune surveillance. Theoretically, reactivation of the EBV antigen expression may potentiate the cell-mediated immunity and complete the viral lytic cycles (3,9,10). Recognition of some of these antigens, notably the LMP-2 and EBNA-1, has also enabled us to set targets for EBV-based immunotherapy. Recently, multiple noncoding microRNAs have been discovered. Although nonprotein encoding in nature, they are thought to deregulate LMP-1 gene expression and its downstream signaling pathway (11,12).

Many other oncogenes and tumor suppression genes specific to NPC have been identified. For example, STAT3 is believed to be an oncogene, which on activation by EBV will promote the invasiveness of tumor cells. Blockade of STAT3 activation by small-molecule inhibitor reduces cell growth and invasiveness in NPC cell lines (13). MET is another candidate oncogene that encodes the hepatocyte growth factor receptor with protein-tyrosine kinase activity that is actively involved in cell proliferation and tumor metastasis. In NPC, overexpression of c-MET protein is relatively common and is associated with poor prognosis in late-stage disease (14).

■ EBV DNA: PROGNOSTICATION AND MONITORING

Antibodies to EBV immunoglobulin A viral capsid antigen (IgA VCA) and early antigen (IgA EA) have been widely used as screening and diagnostic markers for NPC because their titer levels have been shown to correlate with pretreatment tumor burden (15). However, IgA VCA/EA are not good at monitoring treatment response as they often remain high even after disease remission (16). In contrast, EBV DNA, a tumor-derived DNA that can be detected in plasma or serum using real-time polymerase chain reaction, is more reflective

of tumor burden before or after treatment (16) and can be applied clinically to enhance screening efficiency (17), enable earlier diagnosis (18), improve prognostic accuracy (19–22), monitor response during treatment (23), and allow earlier detection of recurrence. (24). High marker level (>500 copies/ml) at 6 weeks after RT is a powerful prognosticator of recurrence (relative risk = 12) (21), whereas pretreatment EBV DNA is a better discriminator of prognosis than conventional tumor-node-metastasis (TNM) staging in stage II NPC (19). The rapid kinetic of EBV DNA and its high correlation with residual tumor burden may help select high-risk patients for adjuvant treatment. Although EBV DNA is excellent at detecting systemic recurrence with a lead time of around 6 months, it is not sensitive enough to detect small-volume local recurrence (25).

■ ADVANCES IN RADIOLOGICAL IMAGING

Magnetic resonance imaging (MRI) has generally replaced computerized tomography (CT) for local tumor staging because of its better soft tissue resolution. MRI also plays an important role in radiotherapy treatment planning because it provides more accurate delineation of tumor target. For metastatic screening, studies do not support routine incorporation of CT thorax, bone scan, or abdominal ultrasonography in average-risk patients because of their low pick-up rate (26–28), which is reserved for high-risk patients with suspicious features of distant metastasis.

^{18}F -fluoro-2-deoxy-D-glucose (^{18}F -FDG) positron emission tomography (PET)/CT is increasingly popular in staging and as a tool to detect tumor persistence or recurrence. Several studies have compared the accuracy of PET/CT and MRI in detecting primary tumor, retropharyngeal nodes, cervical nodes, and distant metastasis, but their results are inconsistent (29–32). For instance, in a study on 52 patients with advanced NPC, King et al reported 54% discordant rate in primary

tumor and cervical nodal metastasis between PET/CT and MRI. In this study, MRI was found to be more able to define the volume of disease in the nasopharynx, skull base, brain, orbit, and the retropharyngeal node, whereas PET/CT did not identify any MRI-missed cervical node or affect the M stage or change the management in any of the patients (30). On the other hand, in another study with larger number of patients ($n = 111$), Ng et al reported that although MRI appears to be superior for assessment of primary tumor and retropharyngeal nodes, PET/CT is more accurate for determining cervical nodal metastasis and is better than conventional work-up for the detection of distant metastasis (29). Confounding factors such as observer dependence, selection of cutoff SUV_{max} value, and inconsistent use of CT contrast may make direct comparison of these data difficult.

Early detection of local recurrence is crucial to successful salvage. However, it is notoriously difficult to diagnose submucosal or deep-seated recurrence by endoscopy alone, and MRI or CT are unable to distinguish postradiotherapy scarring or inflammation from genuine recurrence (33). Controversy remains as to the superiority of PET/CT over MRI on this aspect. In a systematic review of 21 articles, Liu suggested that PET was the best modality for diagnosis of local residual or recurrent NPC (34). In the near future, PET/CT is going to play a more important role in the staging of NPC at diagnosis and at recurrence and in the monitoring of treatment response.

■ ADVANCES IN TREATMENT OF NONMETASTATIC NPC

Two-Dimensional Radiotherapy

External RT has been the mainstay treatment for nonmetastatic NPC since the introduction of mega-voltage machines in the mid-1960s, when the overall survival was only 25% at 5 years. With improvement in simple 2- to 3-field arrangements delivering 60 to 70 Gy 2-dimensional

radiotherapy (2DRT) to the nasopharynx and its regional lymphatics, the overall survival rate between 1970s to 1980s was typically in the order of 50%, with greater than 25% of locoregional failure (35–37). The major drawback of 2DRT is its unnecessary irradiation of abundant normal tissues and any attempt of vital organ sparing, which would inevitably compromise target coverage (38). Further improvement of treatment outcome was seen in the 1990s as a result of advances in diagnostic imaging and use of more aggressive treatment strategies such as RT dose escalation and chemotherapy. In a retrospective analysis on 2687 patients treated during 1996–2000, the majority (more than 90%) of whom were being treated by 2DRT, 32% being staged by MRI, and 23% being given chemotherapy, an overall survival of 75% and local failure-free rate of 85% at 5 years were reported (1). The improvement was most remarkable in the intermediate-risk group, but the outcome of T4 or stage IV patients remained poor.

3-Dimensional Conformal Radiotherapy

The transition from 2DRT to 3-dimensional conformal radiotherapy (3DCRT) marked a great leap in RT development in the late 1990s, and the development of computer planning system and multileaf collimator is the cornerstone for such changes. The integration of CT or MRI images into the 3-dimensional treatment planning system provides more accurate spatial information of tumor target and normal organs, which enables more flexible adjustment of beam direction, while the use of multileaf collimator allows better shaping of beam aperture that conforms to the shape of the target and avoids vital organs in the vicinity. This theoretic dosimetric advantage of 3DCRT in NPC did not translate into significant clinical benefit as shown by Wolden et al, mostly because the conformity achieved by 3DCRT is not good enough to allow optimal target coverage and normal organ sparing (39–41).

Intensity-Modulated Radiotherapy

The use of 3DCRT was rapidly overtaken by the development of intensity-modulated radiotherapy (IMRT), which was started to be clinically used in NPC in the late 1990s. IMRT is an advanced form of 3DCRT with an additional capacity to modulate beam intensity pixel by pixel across the treatment field. Working in conjunction with the inverse planning computer optimization algorithm, an optimized fluence can be obtained according to the dose-volume constraints set by the physicians. It is particularly useful in generating a concave-shaped dose distribution with steep dose gradient around the brainstem, spinal cord, and optic pathway. The principle benefit of IMRT in early-stage NPC is parotid sparing; in locoregionally advanced NPC, it offers better tumor coverage and protection of critical neurological organs and allows room for dose escalation (39,40,42). Moreover, IMRT permits the delivery of different dose intensities to different targets according to their clinical risks and enables biological enhancement through the concept of simultaneous modulated accelerated RT. A comparison of dose distribution between 2DRT and IMRT is demonstrated in Figure 11.1.

There are now at least 9 published clinical studies using IMRT in the literature (Table 11.1) (43–51). Despite their nonrandomized design, limited sample size, and relatively short follow-up time, they consistently reported a high local control rate between 84% and 100% and improvement in xerostomia. Two randomized trials from Hong Kong have compared the xerostomia severity after IMRT or 2DCRT in early-stage NPC, producing similar results supporting the parotid-sparing potential of IMRT (52,53). Disappointingly, despite all these merits, the distant metastasis rate and the overall survival rate have not substantially improved compared with historical control. Nevertheless, in view of the dosimetric advantage and superior local tumor control and toxicity profile, IMRT has rapidly been accepted as the contemporary state-of-the-art RT technique for the treatment of NPC worldwide.

Dose Escalation

Dose escalation has been tested in adjuvant setting in a hope to improve local control. Most common forms of dose escalation techniques include intracavitary brachytherapy (ICB) (54–56), single-dose stereotactic radiosurgical boost (SRS) (57–59), fractionated stereotactic radiotherapy boost (SRT) (60), and IMRT boost. ICB is mainly employed for T1/2 superficial lesions. SRS and SRT boost can achieve high local control rates at 93% to 98% by the Stanford and Taiwan groups (57–60), but the 7% of temporal lobe necrosis and 5% of fatal epistaxis should not be ignored (59,60).

Altered Fractionation

Two randomized studies have evaluated the role of altered fractionation (AF) for NPC. In the first trial, Teo et al randomized patients with N0 or nodal size less than 4 cm to AF or conventional RT (61). The AF took the format of midcourse bid (1.8 to 1.5 Gy) hyper- and accelerated fractionation. There was no difference in local control or overall survival, but the trial was prematurely terminated because of excessive neurological toxicities (49% vs. 23%). The second trial, the NPC-9902 study, confined accrual to a group of T3–4N0–1 patients with predominant risk of local failure to address the potential benefit of concurrent chemotherapy and accelerated fractionation in a 2×2 factorial design (62). There was no benefit for accelerated RT alone. Although progression-free survival seems to have a trend toward improvement with chemotherapy and accelerated RT in combination, the trial was underpowered by being stopped early due to slow accrual. No survival benefit was detected in this study. Until further confirmatory results from prospective randomized studies are available, the use of accelerated fractionation should remain investigational.

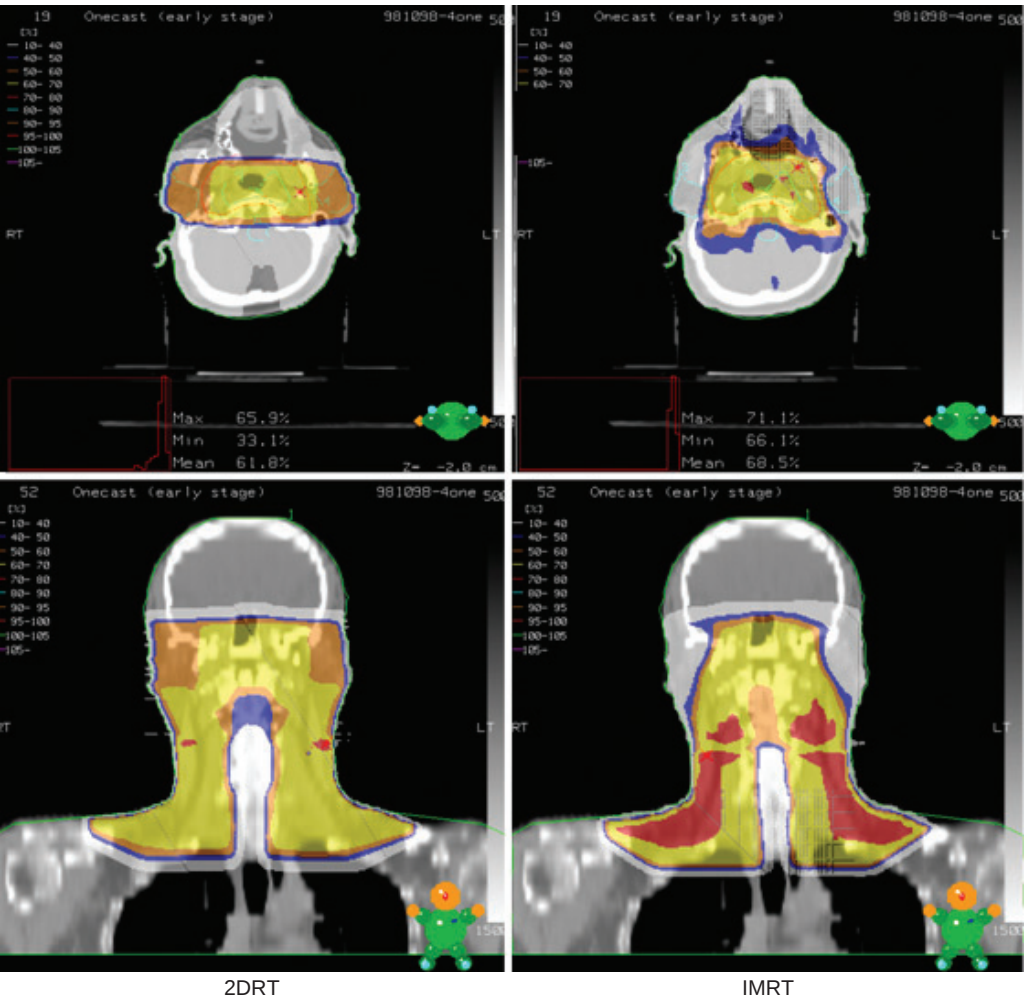


FIGURE 11.1
Comparison of isodose distribution between 2DRT and IMRT.

Chemoradiotherapy

Today, chemotherapy is closely integrated with RT in the treatment of stage III-IV disease. At least 15 randomized trials of chemotherapy and 3 meta-analyses in NPC have reported on the role of neoadjuvant, concurrent, as well as adjuvant chemotherapy (Table 11.2) (62–76). The meta-analysis run by the MAC-NPC Collaborative

Group, using updated individual patient data, confirmed an absolute 6% 5-year overall survival benefit with the addition of chemotherapy, the largest benefit being seen when RT is given in conjunction with concurrent chemotherapy (77). Neoadjuvant chemotherapy could improve locoregional and distant control, though this was not translated into significant benefit in overall survival. Adjuvant chemotherapy was ineffective in all aspects.

TABLE 11.1
Results from series treating NPC with IMRT with or without chemotherapy

Study	N	T Stage	Median Follow-up (mo)	Total dose (Gy)	Dose/ Fraction (Gy)	Time Point (y)	Local Control (%)	Nodal Control (%)	Distant Control (%)	Overall Survival (%)
Lee et al (USA) (43)	118	All	30	70	2.12	4	96	98	72	74
Kam et al (HK) (44)	63	All	29	66	2	3	92	98	79	90
Wolden et al (USA) (45)	74	All	35	70.2	2.34	3	91	93	78	83
Kwong et al (HK) (50)	50	T1/2	14	70	2	3	100	92.3	100	100
Kwong et al (HK) (51)	50	T3/4	25	76	2.17	2	96*	—	94	92
Lee et al (Korea) (48)	20	All	27	72	2.4	2	88*	—	90	NR
Fang et al (Taiwan) (46)	110	All	40	72	2.4	3	84.2*	—	82.6	85.4
Tham et al (Singapore) (49)	195	All	37	70	2.12	3	89.6*	—	89.2	94.3
RTOG0225 (47)	68	All	31	70	2.12	2	92.6	90.8	84.7	80.2

USA, United States of America; HK, Hong Kong; NR, not reported.
*Locoregional control.

TABLE 11.2
Trials of chemotherapy with RT versus RT alone in locally advanced NPC

Author	Treatment Arm	Time Point (year)	Local-oregional Control (%)	Distant Control (%)	Progression- Free Survival (%)	Overall Survival (%)
NEOADJUVANT CHEMOTHERAPY + RT VERSUS RT ALONE						
VUMCA (70)	a	3			52*	60
	b				32	54
Chua et al (72)	a	3			48	78
	b				42	71
Ma et al (73)	a	5			59*	63
	b				49	56
Hareyama et al (71)	a	5			55	60
	b				43	48
CONCURRENT CHEMOTHERAPY + RT VERSUS RT ALONE						
Lin et al (66)	a	5	89*	79 [#]	72*	72*
	b		73	70	53	54
Chan et al (64)	a	5	NS	NS	60	70*
	b				52	59
ADJUVANT CHEMOTHERAPY + RT VERSUS RT ALONE						
Rossi et al (76)	a	5			54	55
	b				50	61
Chi et al (75)	a	4			58	59
	b				56	67
NEOADJUVANT AND ADJUVANT CHEMOTHERAPY + RT VERSUS RT ALONE						
Chan et al (74)	a	2			68	80
	b				72	81
CONCURRENT AND ADJUVANT CHEMOTHERAPY + RT VERSUS RT ALONE						
Al-Sarraf et al (63)	a	5			58*	67*
	b				29	37
Wee et al (67)	a	3		87*	72*	80*
	b			70	53	65
Lee et al (69)	a	3	92*	76	70	78
	b		82	73	61	78
Lee et al (62)	CF RT vs	3	85	81	68	83
	AF RT		78	77	63	73
	CF RT+C		81	89	73	87
	AF RT+C		94	97*	88 [#]	88
Kwong et al (68)	a	3	80	85*	69	87 [#]
	b		72	71	58	77

TR, radiotherapy; a, combined therapy arm; b, radiotherapy alone arm; CF RT, conventional fractionation radiotherapy; AF RT, accelerated fractionated radiotherapy; C, chemotherapy.

[§]Either progression-free survival or disease-free survival are collectively termed progression-free survival.

*Statistically significant ($P < .05$).

#Borderline significance ($P = .05-.08$).

Concurrent Chemoradiation With or Without Adjuvant Chemotherapy

The pivotal trial that prompted oncologists to incorporate chemotherapy into radiotherapy in stage III-IV nonmetastatic NPC is the US Intergroup (0099) trial (63). In this study, 147 patients were randomized to either RT alone or RT with concurrent chemotherapy (3 cycles of cisplatin 100 mg/m²) and adjuvant chemotherapy (3 cycles of cisplatin at 80 mg/m², day 1, and fluorouracil at 1000 mg/m², days 1 to 4). The 5-year overall survival rate was 37% in the RT-alone arm compared with 67% in the chemoradiotherapy arm ($P = .001$). Both locoregional and distant failure rates were also reduced in the combined arm. However, investigators from Asian countries were once skeptical about the validity of the Intergroup-0099 regimen in endemic NPC populations because of the poor results within RT-alone arm, high percentage of World Health Organization type I histology, and poor compliance of adjuvant chemotherapy in this study.

Two studies have compared concurrent chemoradiotherapy versus RT alone. Chan et al randomized patients with Ho's N2, N3, or nodal size greater than 4 cm to receive either weekly low-dose cisplatin (40 mg/m²/wk) and RT or RT alone (64,65). The 5-year overall survival demonstrated an 11% improvement in the combined arm (70% vs. 59%; $P = .048$). Lin et al randomized patients to either RT alone or RT plus 2 cycles of concurrent cisplatin and infusional fluorouracil (66). An improvement of 19% in the 5-year overall survival was noted in the combined arm (53% vs. 72%; $P = .002$).

Apart from the Intergroup-0099 study, 4 more randomized studies have compared RT alone with RT plus concurrent and adjuvant chemotherapy. Wee et al observed a significant improvement in disease-free survival (45% vs. 55%; $P = .04$) and overall survival (46% vs. 65%; $P = .01$) at 5 years, confirming the findings of Intergroup-0099 study (67). Kwong et al conducted a factorial study with 4 arms (RT alone, RT plus concurrent chemotherapy, RT plus adjuvant chemotherapy, and RT plus concurrent and adjuvant chemotherapy) using Uracil-tegafur (UFT) at the concurrent phase and

vinblastine/bleomycin/methotrexate/fluorouracil at the adjuvant phase (68). The long-term result of this study was recently updated, confirming the significant improvement in distant metastasis-free ($P = .014$) and failure-free survival ($P = .016$), and borderline improvement in disease-specific survival ($P = .057$) with concurrent chemotherapy. In contrast, Lee et al randomly assigned patients exclusively with advanced regional disease (N2 or N3) to the identical Intergroup-0099 regimen (69). The chemoradiotherapy arm showed statistically significant improvement in the 3-year failure-free survival (62% vs. 72%; $P = .027$), which did not translate into improvement in overall survival (78% vs. 78%; $P = .97$).

Neoadjuvant Chemotherapy and Concurrent Chemoradiation

Maintaining chemotherapy compliance and chemotherapy dose intensity is vital to achieving good outcome in NPC. The negative result from adjuvant chemotherapy trial and the unclear benefit of adjuvant chemotherapy in the Intergroup-0099 regimen in endemic regions may be explained by the poor compliance rather than any sequence-dependent chemosensitivity. In the trials previously mentioned, chemotherapy compliance rates differed significantly, with the highest compliance being seen in neoadjuvant setting (87%–100%), followed by concurrent chemotherapy (44%–93%), and worst in adjuvant chemotherapy (14%–55%). This argument prompted investigators to switch the sequence of chemotherapy from concurrent-adjuvant to induction-concurrent with a hope to intensify treatment with more modern cytotoxic chemotherapy without compromising drug compliance. Building on these premises, several recent phase II studies have tested the feasibility of using modern cytotoxic agents (infusional fluorouracil, taxanes, interferon) in neoadjuvant setting in NPC, with promising results (24,78–80). Hui et al reported on a randomized phase II study that explored the efficacy and toxicity of adding neoadjuvant docetaxel and cisplatin to concurrent cisplatin-radiotherapy in locoregionally advanced NPC (80). With a median follow-up of 4.7 years, there was an improvement

in overall survival favoring the neoadjuvant arm (94% vs. 68%; $P = .012$), and the acute toxicities were well tolerated. In view of this excellent result, an international phase III trial has been initiated testing induction TPF followed by cisplatin-RT versus cisplatin-RT alone.

■ ADVANCES IN THE TREATMENT OF LOCAL RECURRENCE

Treatment of local recurrence has always been a great challenge to oncologists, although this incidence is declining with the increasing use of IMRT. The TNM stage at the time of local recurrence is the most important factor that dictates the choice of treatment and prognosis. Reirradiation is often the only option that is potentially curative for patients with local failure because most local recurrences tend to be deep seated at the base of skull, where surgical resection is not feasible. Yu et al reported on 319 patients with local failure, of whom 50% had stage T3 to T4 disease at recurrence and more than 80% had isolated local recurrence, the 3-year overall survival rate (defined as the time from primary RT to time of local recurrence) for the entire cohort was 74% (81). The treatment options included external RT, brachytherapy, nasopharyngectomy, and chemotherapy alone. Patients with isolated local failure who received salvage treatment had a significantly better overall survival than the patients who did not receive the treatment. However, subgroup analysis showed that salvage treatment did not improve survival rates in patients with stages T3/4 disease at recurrence. There was also no significant difference in survival between patients treated with radical RT or surgery.

Salvage Surgery

The challenge of skull base or nasopharyngeal surgery is to achieve an adequate surgical margin while preserving the neurovascular bundle. The more commonly used surgical approaches include the transpalatal approach, maxillary swing (82), or midface degloving techniques (83). Positive

surgical margin and dural or brain invasion are poor prognostic factors (84,85). Maxillary swing had less local recurrence than midface degloving in the T1/2 subgroup (86).

Reirradiation

Reirradiation poses a therapeutic challenge for recurrent NPC because the tolerance of normal tissues to cumulative radiation dose is limited. Brachytherapy can deliver a high dose to a small tumor volume and is applicable to tumors confined to the nasopharyngeal cavity and away from the skull base. Using interstitial implants with radioactive gold grains, Kwong et al reported a 5-year local relapse-free rate of 63% (87). Law et al used iridium mold and achieved an excellent 5-year actuarial local control rate of 85% but had a complication rate of 47% (88).

External RT reirradiation is an alternative to brachytherapy and is more appropriate in advanced local recurrence. Stereotactic radiosurgery has been used to treat small-volume T1/2 recurrence (89–92). For more advanced recurrence, fractionated stereotactic radiotherapy is preferred; however, the incidence of late complication is still very high (93–97). Preliminary results on using IMRT has produced encouraging results, but the follow-up time is short (98,99).

■ ADVANCES IN CYTOTOXIC CHEMOTHERAPY IN METASTATIC DISEASE

Distant metastases have been a major cause of treatment failure and death in patients with NPC. The median survival of metastatic NPC varies considerably depending on the site and volume of metastases, and the duration of metastasis-free survival from the time of initial diagnosis. In a retrospective study on 2915 patients treated from 1996 to 2000, Hui et al reported a 14.9% 5-year actuarial rate of distant metastasis in the entire cohort (100). This

study used the overall survival (calculated from the time of primary RT to the time of death) rather than metastatic survival (defined as the time from diagnosis of recurrence to the time of death) as surrogate endpoint and observed that patients with lung metastasis have a much better survival than those with bone or liver metastases and suggested aggressive treatment for maximal prolongation of survival.

Although chemotherapy has never been compared with supportive care alone in metastatic

NPC, platinum-based doublet is a popular choice for this indication because of its association with high response rates and occasional observation of prolonged remission. Table 11.3 gives a summary of selected phase II chemotherapy trials in the first-line treatment of metastatic or recurrent NPC (101–111). Gemcitabine, taxanes, capecitabine, irinotecan, and vinorelbine are some of the modern cytotoxic agents that have shown activity in combination with cisplatin/carboplatin in first-line setting. An excellent response rate

TABLE 11.3
Phase II trials of chemotherapy in first-line treatment of metastatic or recurrent NPC

Author	Sample Size	Regimen	Overall Response (%)	Median time to Progression (months)	Median Survival (months)
Boussen et al. (101)	49	Cisplatin-bleomycin-5FU	78	—	—
Au et al (102)	24	Cisplatin-5FU	66	8	11
Siu et al (103)	90	CAPABLE	80	—	14
Yeo et al (104)	27	Carboplatin-paclitaxel	59	6 (mean)	12
Taamma et al (105)	49	Cisplatin-5FU-bleomycin-epirubicin	78 (metastasis)	—	—
			91 (locally advanced)	—	—
Ngan et al (106)	44	Cisplatin-gemcitabine	73	10.6	15
Chua et al (107)	19	Cisplatin-docetaxel	63	5.6	12.4
Leong et al (108)	32	Carboplatin-paclitaxel-gemcitabine	78	8.1	18.6
Ma et al (109)	41	Oxaliplatin-infusional gemcitabine	56	9	19.6
Chua et al (111)	44	Cisplatin-capecitabine	54	6.8	NR (1 y = 73%)
Li et al (110)	48	Cisplatin-capecitabine	63	7.7	13.3

5FU, 5-fluorouracil; CAPABLE, cyclophosphamide/doxorubicin/cisplatin/methotrexate/bleomycin; NR, not reached.

ranging from 50% to 80% is expected, but progression is common, and the median survival is at best 12 to 20 months, with a median time to progression of 5 to 11 months. In general, multidrug combinations (3 or more drugs) are associated not only with higher response rates and longer time to progression but also with more serious toxicities.

Although platinum has been regarded as the backbone for most first-line regimens for NPC, there are no level I data to show whether cisplatin and carboplatin are interchangeable. Carboplatin is often considered as a substitute for cisplatin in patients with intolerable renal toxicity or ototoxicity. Another platinum compound, oxaliplatin, has proven to be active when used in combination with gemcitabine (GEMOX) (109).

For patients with recurrent or metastatic NPC who are resistant to platinum-based chemotherapy, second-line monotherapy or combinations have reported variable response rates of 14% to 48%, median time to progression of 5 months, and median survival of 7 to 11 months. The list of drugs that are active in this setting is steadily expanding and include agents such as capecitabine (112), irinotecan, vinorelbine (113), and gemcitabine (7,114,115). Obviously, treatment response and chemotherapy tolerance for this group of heavily pretreated patients are expected to be poor. With a potentially superior therapeutic index, molecular targeted agents represent exciting compounds that may complement the use of conventional chemotherapy in this disease.

■ OTHER NOVEL THERAPIES

Molecular Targeted Therapy

Signaling Protein Kinases

The rationale of targeting EGFR in NPC is based on both preclinical and clinical evidence. EGFR is expressed in more than 80% of NPC, and EGFR overexpression is associated with inferior survival (7,115). Inhibition of EGFR ligand binding with monoclonal antibody cetuximab (C225) has been

shown to reduce cell growth in NPC cell lines (116), and additive effect can be seen when cetuximab is combined with cisplatin in vitro (117). Clinically, the combination of cetuximab and cisplatin has been evaluated in a phase II study in 60 patients with metastatic NPC who had failed previous platinum-based regimens. The combination was well tolerated and the overall response rate was 11.7%, with a disease stabilization rate of 48.3%, confirming the activity of cetuximab in this setting. More recently, cetuximab has been evaluated in combination with cisplatin and IMRT in patients with locoregionally advanced NPC. Preliminary results suggested that this strategy is feasible, although there is an increased incidence of mucositis, dysphagia, and radiation dermatitis (118,119).

Gefitinib (Iressa) is a small-molecule inhibitor of the EGFR tyrosine kinase that has been extensively used in non-small cell lung carcinoma. Inhibition of EGFR signaling with gefitinib has been shown in NPC cell lines. However, this has not been translated into clinical benefit based on 2 recently published studies, using gefitinib monotherapy at either 250 or 500 mg daily in chemotherapy refractory patients (120,121). There was no objective response in these studies, and the median time to progression was short at 2.7 to 4 months. To look into the cause of gefitinib resistance in EGFR-expressed situation, preclinical study from our hospital has discovered the cross-talk phenomenon in NPC cell lines on exposure to gefitinib (122). p-AKT activation remains high despite successful suppression of other kinases. Unlike lung or colorectal cancers, EGFR or k-RAS mutation were not detected in the NPC cells.

Hypoxia and Angiogenesis

Tumor hypoxia is associated with resistance to RT and chemotherapy and poorer survival. At the cellular level, hypoxia is known to induce the expression of a transcriptional factor, hypoxia-inducible factor (HIF)-1 α , which then upregulates the expression of downstream genes responsible for acid-base balance and intercellular communication

(carbonic anhydrase 9 [CA-9]) and angiogenesis (vascular endothelial growth factor [VEGF]). In NPC cell lines, upregulation of the expression of HIF-1 α , CA-9, and VEGF was similarly seen in hypoxic environment (123,124), whereas in NPC tissue block, overexpression of these factors strongly correlated with inferior patient survival (124). The osteopontin level in plasma of locoregionally advanced NPC patients did not show significant elevation compared with normal control, although high pretreatment plasma osteopontin level was shown to be a significant predictor of poor response to radiotherapy (125). The feasibility of using these hypoxic biomarkers either as a predictor of response or as a therapeutic target in NPC remains to be defined.

VEGF expression is associated with angiogenesis in many tumor models, including NPC. In NPC, high expression of VEGF has been related to higher rate of recurrence, lymph node metastases, distant metastases, and lower survival (126,127). Bevacizumab is a recombinant humanized IgG1 monoclonal antibody against VEGF and has inhibitory effect on tumor angiogenesis. Clinically, bevacizumab has been evaluated in combination with IMRT and cisplatin in stage IIB-IVB NPC in a Radiation Therapy Oncology Group (RTOG) phase II study.

Epigenetic Therapy

CpG methylation is associated with silencing of EBV immunodominant antigens and tumor suppressor genes. Therapies that demethylate the genes or antigens may have the potential to restore the normal cell growth and reactivate the host's immune response against the virus. The demethylating agent 5-azacitidine was shown to consistently achieve demethylation of the promoter regions in EBV genes but failed to upregulate the immunodominant antigens (128). The combination of 5-azacitidine and a histone deacetylase inhibitor is being investigated by an NCI study to test the hypothesis that reversal of both methylation and histone deacetylation may lead to a greater degree

of gene transcription than the reversal of one mechanism alone.

EBV-Based Immunotherapy

The presence of EBV antigens in tumor cells provides a target for immunotherapy. However, immunotherapy against NPC requires cytotoxic T lymphocytes (CTL) that recognize some of the subdominant viral antigens such as the EBNA-1 and LMP-1 and -2 (129). Adoptive transfer of CTL specific for LMP-2 and EBNA-1 has been tested with limited success (130). Antitumor response could be further enhanced by pulsing the dendritic cells with peptides derived from LMP-2 (131). Autologous CTL therapy was used to treat 10 NPC patients with very promising results (132).

CONCLUSIONS

Major advances in the multidisciplinary management of NPC have been translated into improvement in survival over the past few decades. Technological development in diagnostic imaging has resulted in more accurate detection of tumor, whereas application of plasma EBV DNA provides a sensitive tool for disease monitoring. Clinical trials have proven the value of chemotherapy and radiotherapy both in organ-confined and metastatic setting. Nevertheless, we are still facing a high percentage of metastatic failure, which are unlikely curable with the existing treatment modalities. In future, the treatment strategies for NPC will likely incorporate the use of targeted agents, genetic and epigenetic therapy, as well as EBV-based immunotherapy.

KEY POINTS

- Highlight on the distinctive histological and epidemiological features of NPC as compared with other squamous cell carcinoma of head and neck region.

- Highlight on the genetic and epigenetic alterations in pathogenesis of NPC.
- Role of EBV in the pathogenesis of NPC and clinical application of plasma EBV DNA.
- Role of magnetic resonance imaging and positron emission tomography-computed tomography in staging and radiotherapy planning.
- Discussion on the two major modalities, radiotherapy and chemotherapy, in curative treatment of nonmetastatic NPC. Clinical evidence from phase II and III trials.
- Role of external beam reirradiation, brachytherapy, and salvage surgery in the management of local recurrence.
- The current approach of using different combinations of systemic chemotherapy in the management of distant metastasis.
- Discussion on the preclinical and clinical evidence of different novel therapies, including molecular target therapy, epigenetic therapy, and immunotherapy.

REFERENCES

1. Lee AW, Sze WM, Au JS, et al. Treatment results for nasopharyngeal carcinoma in the modern era: the Hong Kong experience. *Int J Radiat Oncol Biol Phys.* 2005;61(4):1107–1116.
2. Tao Q, Chan AT. Nasopharyngeal carcinoma: molecular pathogenesis and therapeutic developments. *Expert Rev Mol Med.* 2007;9(12):1–24.
3. Ambinder RF, Robertson KD, Moore SM, Yang J. Epstein-Barr virus as a therapeutic target in Hodgkin's disease and nasopharyngeal carcinoma. *Semin Cancer Biol.* 1996;7(4):217–226.
4. Chan AT, Teo PM, Huang DP. Pathogenesis and treatment of nasopharyngeal carcinoma. *Semin Oncol.* 2004;31(6):794–801.
5. Hui AB, Lo KW, Teo PM, To KF, Huang DP. Genome wide detection of oncogene amplifications in nasopharyngeal carcinoma by array based comparative genomic hybridization. *Int J Oncol.* 2002;20(3):467–473.
6. Miller WE, Earp HS, Raab-Traub N. The Epstein-Barr virus latent membrane protein 1 induces expression of the epidermal growth factor receptor. *J Virol.* 1995;69(7):4390–4398.
7. Ma BB, Poon TC, To KF, et al. Prognostic significance of tumor angiogenesis, Ki 67, p53 oncoprotein, epidermal growth factor receptor and HER2 receptor protein expression in undifferentiated nasopharyngeal carcinoma—a prospective study. *Head Neck.* 2003;25(10):864–872.
8. Leong JL, Loh KS, Putti TC, Goh BC, Tan LK. Epidermal growth factor receptor in undifferentiated carcinoma of the nasopharynx. *Laryngoscope.* 2004;114(1):153–157.
9. Westphal EM, Blackstock W, Feng W, Israel B, Kenney SC. Activation of lytic Epstein-Barr virus (EBV) infection by radiation and sodium butyrate in vitro and in vivo: a potential method for treating EBV-positive malignancies. *Cancer Res.* 2000;60(20):5781–5788.
10. Moore SM, Cannon JS, Tanhehco YC, Hamzeh FM, Ambinder RF. Induction of Epstein-Barr virus kinases to sensitize tumor cells to nucleoside analogues. *Antimicrob Agents Chemother.* 2001;45(7):2082–2091.
11. Lo AK, To KF, Lo KW, et al. Modulation of LMP1 protein expression by EBV-encoded microRNAs. *Proc Natl Acad Sci U S A.* 2007;104(41):16164–16169.
12. Chen HC, Chen GH, Chen YH, et al. MicroRNA deregulation and pathway alterations in nasopharyngeal carcinoma. *Br J Cancer.* 2009;100(6):1002–1011.
13. Lui VW, Wong EY, Ho Y, et al. STAT3 activation contributes directly to Epstein-Barr virus-mediated invasiveness of nasopharyngeal cancer cells in vitro. *Int J Cancer.* 2009;125(8):1884–1893.
14. Qian CN, Guo X, Cao B, et al. Met protein expression level correlates with survival in patients with late-stage nasopharyngeal carcinoma. *Cancer Res.* 2002;62(2):589–596.
15. Henle G, Henle W. Epstein-Barr virus-specific IgA serum antibodies as an outstanding feature of nasopharyngeal carcinoma. *Int J Cancer.* 1976;17(1):1–7.
16. Shao JY, Li YH, Gao HY, et al. Comparison of plasma Epstein-Barr virus (EBV) DNA levels and serum EBV immunoglobulin A/virus capsid antigen antibody titers in patients with nasopharyngeal carcinoma. *Cancer.* 2004;100(6):1162–1170.
17. Leung SF, Tam JS, Chan AT, et al. Improved accuracy of detection of nasopharyngeal carcinoma by combined application of circulating Epstein-Barr virus DNA and anti-Epstein-Barr viral capsid antigen IgA antibody. *Clin Chem.* 2004;50(2):339–345.
18. Lo YM. Quantitative analysis of Epstein-Barr virus DNA in plasma and serum: applications to tumor detection and monitoring. *Ann NY Acad Sci.* 2001;945:68–72.
19. Leung SF, Zee B, Ma BB, et al. Plasma Epstein-Barr viral deoxyribonucleic acid quantitation

- complements tumor-node-metastasis staging prognostication in nasopharyngeal carcinoma. *J Clin Oncol*. 2006;24(34):5414–5418.
20. Leung SF, Chan AT, Zee B, et al. Pretherapy quantitative measurement of circulating Epstein-Barr virus DNA is predictive of posttherapy distant failure in patients with early-stage nasopharyngeal carcinoma of undifferentiated type. *Cancer*. 2003;98(2):288–291.
 21. Chan AT, Lo YM, Zee B, et al. Plasma Epstein-Barr virus DNA and residual disease after radiotherapy for undifferentiated nasopharyngeal carcinoma. *J Natl Cancer Inst*. 2002;94(21):1614–1619.
 22. Lin JC, Wang WY, Chen KY, et al. Quantification of plasma Epstein-Barr virus DNA in patients with advanced nasopharyngeal carcinoma. *N Engl J Med*. 2004;350(24):2461–2470.
 23. Lo YM, Leung SF, Chan LY, et al. Kinetics of plasma Epstein-Barr virus DNA during radiation therapy for nasopharyngeal carcinoma. *Cancer Res*. 2000;60(9):2351–2355.
 24. Chan AT, Ma BB, Lo YM, et al. Phase II study of neo-adjuvant carboplatin and paclitaxel followed by radiotherapy and concurrent cisplatin in patients with locoregionally advanced nasopharyngeal carcinoma: therapeutic monitoring with plasma Epstein-Barr virus DNA. *J Clin Oncol*. 2004;22(15):3053–3060.
 25. Leung SF, Lo YM, Chan AT, et al. Disparity of sensitivities in detection of radiation-naïve and postirradiation recurrent nasopharyngeal carcinoma of the undifferentiated type by quantitative analysis of circulating Epstein-Barr virus DNA1,2. *Clin Cancer Res*. 2003;9(9):3431–3434.
 26. Leung SF, Stewart IE, Tsao SY, Metreweli C. Staging bone scintigraphy in nasopharyngeal carcinoma. *Clin Radiol*. 1991;43(5):314–315.
 27. Leung SF, Metreweli C, Tsao SY, Van Hasselt CA. Staging abdominal ultrasonography in nasopharyngeal carcinoma. *Australas Radiol*. 1991;35(1):31–32.
 28. Leung S, Cheung H, Teo P, Lam WW. Staging computed tomography of the thorax for nasopharyngeal carcinoma. *Head Neck*. 2000;22(4):369–372.
 29. Ng SH, Chan SC, Yen TC, et al. Staging of untreated nasopharyngeal carcinoma with PET/CT: comparison with conventional imaging work-up. *Eur J Nucl Med Mol Imaging*. 2009;36(1):12–22.
 30. King AD, Ma BB, Yau YY, et al. The impact of 18F-FDG PET/CT on assessment of nasopharyngeal carcinoma at diagnosis. *Br J Radiol*. 2008;81(964):291–298.
 31. Chen YK, Su CT, Ding HJ, et al. Clinical usefulness of fused PET/CT compared with PET alone or CT alone in nasopharyngeal carcinoma patients. *Anticancer Res*. 2006;26(2B):1471–1477.
 32. Gordin A, Golz A, Daitzchman M, et al. Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography imaging in patients with carcinoma of the nasopharynx: diagnostic accuracy and impact on clinical management. *Int J Radiat Oncol Biol Phys*. 2007;68(2):370–376.
 33. Comoretto M, Balestreri L, Borsatti E, Cimitan M, Franchin G, Lise M. Detection and restaging of residual and/or recurrent nasopharyngeal carcinoma after chemotherapy and radiation therapy: comparison of MR imaging and FDG PET/CT. *Radiology*. 2008;249(1):203–211.
 34. Liu T, Xu W, Yan WL, Ye M, Bai YR, Huang G. FDG-PET, CT, MRI for diagnosis of local residual or recurrent nasopharyngeal carcinoma, which one is the best? A systematic review. *Radiother Oncol*. 2007;85(3):327–335.
 35. Lee AW, Poon YF, Foo W, et al. Retrospective analysis of 5037 patients with nasopharyngeal carcinoma treated during 1976–1985: overall survival and patterns of failure. *Int J Radiat Oncol Biol Phys*. 1992;23(2):261–270.
 36. Teo P, Yu P, Lee WY, et al. Significant prognosticators after primary radiotherapy in 903 nondisseminated nasopharyngeal carcinoma evaluated by computer tomography. *Int J Radiat Oncol Biol Phys*. 1996;36(2):291–304.
 37. Geara FB, Sanguineti G, Tucker SL, et al. Carcinoma of the nasopharynx treated by radiotherapy alone: determinants of distant metastasis and survival. *Radiother Oncol*. 1997;43(1):53–61.
 38. Chau RM, Teo PM, Choi PH, Cheung KY, Lee WY. Three-dimensional dosimetric evaluation of a conventional radiotherapy technique for treatment of nasopharyngeal carcinoma. *Radiother Oncol*. 2001;58(2):143–153.
 39. Kam MK, Chau RM, Suen J, Choi PH, Teo PM. Intensity-modulated radiotherapy in nasopharyngeal carcinoma: dosimetric advantage over conventional plans and feasibility of dose escalation. *Int J Radiat Oncol Biol Phys*. 2003;56(1):145–157.
 40. Hunt MA, Zelefsky MJ, Wolden S, et al. Treatment planning and delivery of intensity-modulated radiation therapy for primary nasopharynx cancer. *Int J Radiat Oncol Biol Phys*. 2001;49(3):623–632.
 41. Wolden SL, Zelefsky MJ, Hunt MA, et al. Failure of a 3D conformal boost to improve radiotherapy for nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys*. 2001;49(5):1229–1234.
 42. Cheng JC, Chao KS, Low D. Comparison of intensity modulated radiation therapy (IMRT) treatment techniques for nasopharyngeal carcinoma. *Int J Cancer*. 2001;96(2):126–131.
 43. Lee N, Xia P, Quivey JM, et al. Intensity-modulated radiotherapy in the treatment of nasopharyngeal

- carcinoma: an update of the UCSF experience. *Int J Radiat Oncol Biol Phys.* 2002;53(1):12–22.
44. Kam MK, Teo PM, Chau RM, et al. Treatment of nasopharyngeal carcinoma with intensity-modulated radiotherapy: the Hong Kong experience. *Int J Radiat Oncol Biol Phys.* 2004;60(5):1440–1450.
 45. Wolden SL, Chen WC, Pfister DG, Kraus DH, Berry SL, Zelefsky MJ. Intensity-modulated radiation therapy (IMRT) for nasopharynx cancer: update of the Memorial Sloan-Kettering experience. *Int J Radiat Oncol Biol Phys.* 2006;64(1):57–62.
 46. Fang FM, Chien CY, Tsai WL, et al. Quality of life and survival outcome for patients with nasopharyngeal carcinoma receiving three-dimensional conformal radiotherapy vs. intensity-modulated radiotherapy—a longitudinal study. *Int J Radiat Oncol Biol Phys.* 2008;72(2):356–364.
 47. Lee N, Harris J, Garden AS, et al. Intensity-modulated radiation therapy with or without chemotherapy for nasopharyngeal carcinoma: radiation therapy oncology group phase II trial 0225. *J Clin Oncol.* 2009;27(22):3684–3690.
 48. Lee SW, Back GM, Yi BY, et al. Preliminary results of a phase I/II study of simultaneous modulated accelerated radiotherapy for nondisseminated nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys.* 2006;65(1):152–160.
 49. Tham IW, Hee SW, Yeo RM, et al. Treatment of nasopharyngeal carcinoma using intensity-modulated radiotherapy—the national cancer centre singapore experience. *Int J Radiat Oncol Biol Phys.* 2009;75(5):1481–1486.
 50. Kwong DL, Pow EH, Sham JS, et al. Intensity-modulated radiotherapy for early-stage nasopharyngeal carcinoma: a prospective study on disease control and preservation of salivary function. *Cancer.* 2004;101(7):1584–1593.
 51. Kwong DL, Sham JS, Leung LH, et al. Preliminary results of radiation dose escalation for locally advanced nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys.* 2006;64(2):374–381.
 52. Kam MK, Leung SF, Zee B, et al. Prospective randomized study of intensity-modulated radiotherapy on salivary gland function in early-stage nasopharyngeal carcinoma patients. *J Clin Oncol.* 2007;25(31):4873–4879.
 53. Pow EH, Kwong DL, McMillan AS, et al. Xerostomia and quality of life after intensity-modulated radiotherapy vs. conventional radiotherapy for early-stage nasopharyngeal carcinoma: initial report on a randomized controlled clinical trial. *Int J Radiat Oncol Biol Phys.* 2006;66(4):981–991.
 54. Levendag PC, Lagerwaard FJ, de Pan C, et al. High-dose, high-precision treatment options for boosting cancer of the nasopharynx. *Radiother Oncol.* 2002;63(1):67–74.
 55. Teo PM, Leung SF, Lee WY, Zee B. Intracavitary brachytherapy significantly enhances local control of early T-stage nasopharyngeal carcinoma: the existence of a dose-tumor-control relationship above conventional tumoricidal dose. *Int J Radiat Oncol Biol Phys.* 2000;46(2):445–458.
 56. Yeo R, Fong KW, Hee SW, Chua ET, Tan T, Wee J. Brachytherapy boost for T1/T2 nasopharyngeal carcinoma. *Head Neck.* 2009;31(12):1610–1618.
 57. Chang SD, Tate DJ, Goffinet DR, Martin DP, Adler JR Jr. Treatment of nasopharyngeal carcinoma: stereotactic radiosurgical boost following fractionated radiotherapy. *Stereotact Funct Neurosurg.* 1999;73(1–4):64–67.
 58. Cmelak AJ, Cox RS, Adler JR, Fee WE Jr, Goffinet DR. Radiosurgery for skull base malignancies and nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys.* 1997;37(5):997–1003.
 59. Hara W, Loo BW Jr, Goffinet DR, et al. Excellent local control with stereotactic radiotherapy boost after external beam radiotherapy in patients with nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys.* 2008;71(2):393–400.
 60. Chen HHW, Tsai ST, Wang MS, et al. Experience in fractionated stereotactic body radiation therapy boost for newly diagnosed nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys.* 2006;66(5):1408–1414.
 61. Teo PM, Leung SF, Chan AT, et al. Final report of a randomized trial on altered-fractionated radiotherapy in nasopharyngeal carcinoma prematurely terminated by significant increase in neurologic complications. *Int J Radiat Oncol Biol Phys.* 2000;48(5):1311–1322.
 62. Lee AW, Tung SY, Chan AT, et al. Preliminary results of a randomized study (NPC-9902 Trial) on therapeutic gain by concurrent chemotherapy and/or accelerated fractionation for locally advanced nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys.* 2006;66(1):142–151.
 63. Al-Sarraf M, LeBlanc M, Giri PG, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. *J Clin Oncol.* 1998;16(4):1310–1317.
 64. Chan AT, Leung SF, Ngan RK, et al. Overall survival after concurrent cisplatin-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma. *J Natl Cancer Inst.* 2005;97(7):536–539.
 65. Chan AT, Teo PM, Ngan RK, et al. Concurrent chemotherapy-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: progression-free survival analysis of a phase III randomized trial. *J Clin Oncol.* 2002;20(8):2038–2044.

66. Lin JC, Jan JS, Hsu CY, Liang WM, Jiang RS, Wang WY. Phase III study of concurrent chemoradiotherapy versus radiotherapy alone for advanced nasopharyngeal carcinoma: positive effect on overall and progression-free survival. *J Clin Oncol*. 2003;21(4):631–637.
67. Wee J, Tan EH, Tai BC, et al. Randomized trial of radiotherapy versus concurrent chemoradiotherapy followed by adjuvant chemotherapy in patients with American Joint Committee on Cancer/International Union against cancer stage III and IV nasopharyngeal cancer of the endemic variety. *J Clin Oncol*. 2005;23(27):6730–6738.
68. Kwong DL, Sham JS, Au GK, et al. Concurrent and adjuvant chemotherapy for nasopharyngeal carcinoma: a factorial study. *J Clin Oncol*. 2004;22(13):2643–2653.
69. Lee AW, Lau WH, Tung SY, et al. Preliminary results of a randomized study on therapeutic gain by concurrent chemotherapy for regionally-advanced nasopharyngeal carcinoma: NPC-9901 Trial by the Hong Kong Nasopharyngeal Cancer Study Group. *J Clin Oncol*. 2005;23(28):6966–6975.
70. Preliminary results of a randomized trial comparing neoadjuvant chemotherapy (cisplatin, epirubicin, bleomycin) plus radiotherapy vs. radiotherapy alone in stage IV(> or = N2, M0) undifferentiated nasopharyngeal carcinoma: a positive effect on progression-free survival. International Nasopharynx Cancer Study Group. VUMCA I trial. *Int J Radiat Oncol Biol Phys*. 1996;35(3):463–469.
71. Hareyama M, Sakata K, Shirato H, et al. A prospective, randomized trial comparing neoadjuvant chemotherapy with radiotherapy alone in patients with advanced nasopharyngeal carcinoma. *Cancer*. 2002;94(8):2217–2223.
72. Chua DT, Sham JS, Choy D, et al. Preliminary report of the Asian-Oceanian Clinical Oncology Association randomized trial comparing cisplatin and epirubicin followed by radiotherapy versus radiotherapy alone in the treatment of patients with locoregionally advanced nasopharyngeal carcinoma. Asian-Oceanian Clinical Oncology Association Nasopharynx Cancer Study Group. *Cancer*. 1998;83(11):2270–2283.
73. Ma J, Mai HQ, Hong MH, et al. Results of a prospective randomized trial comparing neoadjuvant chemotherapy plus radiotherapy with radiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma. *J Clin Oncol*. 2001;19(5):1350–1357.
74. Chan AT, Teo PM, Leung TW, et al. A prospective randomized study of chemotherapy adjunctive to definitive radiotherapy in advanced nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys*. 1995;33(3):569–577.
75. Chi KH, Chang YC, Guo WY, et al. A phase III study of adjuvant chemotherapy in advanced nasopharyngeal carcinoma patients. *Int J Radiat Oncol Biol Phys*. 2002;52(5):1238–1244.
76. Rossi A, Molinari R, Boracchi P, et al. Adjuvant chemotherapy with vincristine, cyclophosphamide, and doxorubicin after radiotherapy in local-regional nasopharyngeal cancer: results of a 4-year multicenter randomized study. *J Clin Oncol*. 1988;6(9):1401–1410.
77. Baujat B, Audry H, Bourhis J, et al. Chemotherapy in locally advanced nasopharyngeal carcinoma: an individual patient data meta-analysis of eight randomized trials and 1753 patients. *Int J Radiat Oncol Biol Phys*. 2006;64(1):47–56.
78. Rischin D, Corry J, Smith J, Stewart J, Hughes P, Peters L. Excellent disease control and survival in patients with advanced nasopharyngeal cancer treated with chemoradiation. *J Clin Oncol*. 2002;20(7):1845–1852.
79. Oh JL, Vokes EE, Kies MS, et al. Induction chemotherapy followed by concomitant chemoradiotherapy in the treatment of locoregionally advanced nasopharyngeal cancer. *Ann Oncol*. 2003;14(4):564–549.
80. Hui EP, Ma BB, Leung SF, et al. Randomized phase II trial of concurrent cisplatin-radiotherapy with or without neoadjuvant docetaxel and cisplatin in advanced nasopharyngeal carcinoma. *J Clin Oncol*. 2009;27(2):242–249.
81. Yu KH, Leung SF, Tung SY, et al. Survival outcome of patients with nasopharyngeal carcinoma with first local failure: a study by the Hong Kong Nasopharyngeal Carcinoma Study Group. *Head Neck*. 2005;27(5):397–405.
82. Wei WI, Ho CM, Yuen PW, Fung CF, Sham JS, Lam KH. Maxillary swing approach for resection of tumors in and around the nasopharynx. *Arch Otolaryngol Head Neck Surg*. 1995;121(6):638–642.
83. To EW, Lai EC, Cheng JH, Pang PC, Williams MD, Teo PM. Nasopharyngectomy for recurrent nasopharyngeal carcinoma: a review of 31 patients and prognostic factors. *Laryngoscope*. 2002;112(10):1877–1882.
84. Vlantis AC, Tsang RK, Yu BK, et al. Nasopharyngectomy and surgical margin status: a survival analysis. *Arch Otolaryngol Head Neck Surg*. 2007;133(12):1296–1301.
85. Hao SP, Tsang NM, Chang KP, Hsu YS, Chen CK, Fang KH. Nasopharyngectomy for recurrent nasopharyngeal carcinoma: a review of 53 patients and prognostic factors. *Acta Otolaryngol*. 2008;128(4):473–481.
86. Vlantis AC, Yu BK, Kam MK, et al. Nasopharyngectomy: does the approach to the nasopharynx influence survival? *Otolaryngol Head Neck Surg*. 2008;139(1):40–46.

87. Kwong DL, Wei WI, Cheng AC, et al. Long term results of radioactive gold grain implantation for the treatment of persistent and recurrent nasopharyngeal carcinoma. *Cancer*. 2001;91(6):1105–1113.
88. Law SC, Lam WK, Ng MF, Au SK, Mak WT, Lau WH. Reirradiation of nasopharyngeal carcinoma with intracavitary mold brachytherapy: an effective means of local salvage. *Int J Radiat Oncol Biol Phys*. 2002;54(4):1095–1113.
89. Chang JT, See LC, Liao CT, et al. Locally recurrent nasopharyngeal carcinoma. *Radiother Oncol*. 2000;54(2):135–142.
90. Chen HJ, Leung SW, Su CY. Linear accelerator based radiosurgery as a salvage treatment for skull base and intracranial invasion of recurrent nasopharyngeal carcinomas. *Am J Clin Oncol*. 2001;24(3):255–258.
91. Chua DT, Sham JS, Kwong PW, Hung KN, Leung LH. Linear accelerator-based stereotactic radiosurgery for limited, locally persistent, and recurrent nasopharyngeal carcinoma: efficacy and complications. *Int J Radiat Oncol Biol Phys*. 2003;56(1):177–183.
92. Low JS, Chua ET, Gao F, Wee JT. Stereotactic radiosurgery plus intracavitary irradiation in the salvage of nasopharyngeal carcinoma. *Head Neck*. 2006;28(4):321–329.
93. Ahn YC, Kim DY, Huh SJ, Baek CH, Park K. Fractionated stereotactic radiation therapy for locally recurrent nasopharynx cancer: report of three cases. *Head Neck*. 1999;21(4):338–345.
94. Leung TW, Wong VY, Tung SY. Stereotactic radiotherapy for locally recurrent nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys*. 2009.
95. Orecchia R, Redda MG, Ragona R, et al. Results of hypofractionated stereotactic re-irradiation on 13 locally recurrent nasopharyngeal carcinomas. *Radiother Oncol*. 1999;53(1):23–28.
96. Wu SX, Chua DT, Deng ML, et al. Outcome of fractionated stereotactic radiotherapy for 90 patients with locally persistent and recurrent nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys*. 2007;69(3):761–769.
97. Chua DT, Wu SX, Lee V, Tsang J. Comparison of single versus fractionated dose of stereotactic radiotherapy for salvaging local failures of nasopharyngeal carcinoma: a matched-cohort analysis. *Head Neck Oncol*. 2009;1(1):13.
98. Lu TX, Mai WY, Teh BS, et al. Initial experience using intensity-modulated radiotherapy for recurrent nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys*. 2004;58(3):682–687.
99. Chua DT, Sham JS, Leung LH, Au GK. Re-irradiation of nasopharyngeal carcinoma with intensity-modulated radiotherapy. *Radiother Oncol*. 2005;77(3):290–294.
100. Hui EP, Leung SF, Au JS, et al. Lung metastasis alone in nasopharyngeal carcinoma: a relatively favorable prognostic group. a study by the hong kong nasopharyngeal carcinoma study group. *Cancer*. 2004;101(2):300–306.
101. Bousсен H, Cvitkovic E, Wendling JL, et al. Chemotherapy of metastatic and/or recurrent undifferentiated nasopharyngeal carcinoma with cisplatin, bleomycin, and fluorouracil. *J Clin Oncol*. 1991;9(9):1675–1681.
102. Au E, Ang PT. A phase II trial of 5-fluorouracil and cisplatin in recurrent or metastatic nasopharyngeal carcinoma. *Ann Oncol*. 1994;5(1):87–89.
103. Siu LL, Czakowski PM, Tannock IF. Phase I/II study of the CAPABLE regimen for patients with poorly differentiated carcinoma of the nasopharynx. *J Clin Oncol*. 1998;16(7):2514–2521.
104. Yeo W, Leung TW, Chan AT, et al. A phase II study of combination paclitaxel and carboplatin in advanced nasopharyngeal carcinoma. *Eur J Cancer*. 1998;34(13):2027–2031.
105. Taamma A, Fandi A, Azli N, et al. Phase II trial of chemotherapy with 5-fluorouracil, bleomycin, epirubicin, and cisplatin for patients with locally advanced, metastatic, or recurrent undifferentiated carcinoma of the nasopharyngeal type. *Cancer*. 1999;86(7):1101–1108.
106. Ngan RK, Yiu HH, Lau WH, et al. Combination gemcitabine and cisplatin chemotherapy for metastatic or recurrent nasopharyngeal carcinoma: report of a phase II study. *Ann Oncol*. 2002;13(8):1252–1258.
107. Chua DT, Sham JS, Au GK. A phase II study of docetaxel and cisplatin as first-line chemotherapy in patients with metastatic nasopharyngeal carcinoma. *Oral Oncol*. 2005;41(6):589–595.
108. Leong SS, Wee J, Tay MH, et al. Paclitaxel, carboplatin, and gemcitabine in metastatic nasopharyngeal carcinoma: a Phase II trial using a triplet combination. *Cancer*. 2005;103(3):569–575.
109. Ma BB, Hui EP, Wong SC, et al. Multicenter phase II study of gemcitabine and oxaliplatin in advanced nasopharyngeal carcinoma—correlation with excision repair cross-complementing-1 polymorphisms. *Ann Oncol*. 2009;20(11):1854–1859.
110. Li YH, Wang FH, Jiang WQ, et al. Phase II study of capecitabine and cisplatin combination as first-line chemotherapy in Chinese patients with metastatic nasopharyngeal carcinoma. *Cancer Chemother Pharmacol*. 2008;62(3):539–544.

111. Chua D, Ng W, Yiu H, et al. Phase II trial of first-line capecitabine plus cisplatin in patients with advanced/metastatic nasopharyngeal cancer (NPC) [Meeting Abstracts]. *J Clin Oncol*. 2008;26(15suppl):6033–6034.
112. Chua D, Wei WI, Sham JS, Au GK. Capecitabine monotherapy for recurrent and metastatic nasopharyngeal cancer. *Jpn J Clin Oncol*. 2008;38(4):244–249.
113. Wang CC, Chang JY, Liu TW, Lin CY, Yu YC, Hong RL. Phase II study of gemcitabine plus vinorelbine in the treatment of cisplatin-resistant nasopharyngeal carcinoma. *Head Neck* 2006;28(1):74–80.
114. Foo KF, Tan EH, Leong SS, et al. Gemcitabine in metastatic nasopharyngeal carcinoma of the undifferentiated type. *Ann Oncol*. 2002;13(1):150–156.
115. Chua DT, Nicholls JM, Sham JS, Au GK. Prognostic value of epidermal growth factor receptor expression in patients with advanced stage nasopharyngeal carcinoma treated with induction chemotherapy and radiotherapy. *Int J Radiat Oncol Biol Phys*. 2004;59(1):11–20.
116. Hsu CH, Gao M, Chen CL, Yeh PY, Cheng AL. Inhibitors of epidermoid growth factor receptor suppress cell growth and enhance chemosensitivity of nasopharyngeal cancer cells in vitro. *Oncology*. 2005;68(4–6):538–547.
117. Sung FL, Poon TC, Hui EP, et al. Antitumor effect and enhancement of cytotoxic drug activity by cetuximab in nasopharyngeal carcinoma cells. *In Vivo*. 2005;19(1):237–245.
118. Kam MK Sr, Ma BB, Leung SF, et al. Dose-volume analysis of radiation dermatitis among nasopharyngeal carcinoma patients treated with concurrent cetuximab-cisplatin and intensity-modulated radiotherapy [Meeting Abstracts]. *J Clin Oncol*. 2008;26(15)(suppl):17015.
119. Ma BB, Leung SF, Kam MK, et al. A phase II study of concurrent cetuximab-cisplatin and intensity-modulated radiotherapy (IMRT) in locoregionally advanced nasopharyngeal carcinoma (NPC) with correlation using dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) [Meeting Abstracts]. *J Clin Oncol*. 2008;26(15 suppl):6055-.
120. Chua DT, Wei WI, Wong MP, Sham JS, Nicholls J, Au GK. Phase II study of gefitinib for the treatment of recurrent and metastatic nasopharyngeal carcinoma. *Head Neck*. 2008;30(7):863–867.
121. Ma B, Hui EP, King A, et al. A phase II study of patients with metastatic or locoregionally recurrent nasopharyngeal carcinoma and evaluation of plasma Epstein-Barr virus DNA as a biomarker of efficacy. *Cancer Chemother Pharmacol*. 2008;62(1):59–64.
122. Ma BB, Lui VW, Poon FF, et al. Preclinical activity of gefitinib in non-keratinizing nasopharyngeal carcinoma cell lines and biomarkers of response. *Invest New Drugs*. 2010;28(3):326–333.
123. Sung FL, Hui EP, Tao Q, et al. Genome-wide expression analysis using microarray identified complex signaling pathways modulated by hypoxia in nasopharyngeal carcinoma. *Cancer Lett*. 2007;253(1):74–88.
124. Hui EP, Chan AT, Pezzella F, et al. Coexpression of hypoxia-inducible factors 1alpha and 2alpha, carbonic anhydrase IX, and vascular endothelial growth factor in nasopharyngeal carcinoma and relationship to survival. *Clin Cancer Res*. 2002;8(8):2595–2604.
125. Hui EP, Sung FL, Yu BK, et al. Plasma osteopontin, hypoxia, and response to radiotherapy in nasopharyngeal cancer. *Clin Cancer Res*. 2008;14(21):7080–7087.
126. Krishna SM, James S, Balaram P. Expression of VEGF as prognosticator in primary nasopharyngeal cancer and its relation to EBV status. *Virus Res*. 2006;115(1):85–90.
127. Wakisaka N, Wen QH, Yoshizaki T, et al. Association of vascular endothelial growth factor expression with angiogenesis and lymph node metastasis in nasopharyngeal carcinoma. *Laryngoscope*. 1999;109(5):810–814.
128. Chan AT, Tao Q, Robertson KD, et al. Azacitidine induces demethylation of the Epstein-Barr virus genome in tumors. *J Clin Oncol*. 2004;22(8):1373–1381.
129. Lee SP, Tierney RJ, Thomas WA, Brooks JM, Rickinson AB. Conserved CTL epitopes within EBV latent membrane protein 2: a potential target for CTL-based tumor therapy. *J Immunol*. 1997;158(7):3325–3334.
130. Chua D, Huang J, Zheng B, et al. Adoptive transfer of autologous Epstein-Barr virus-specific cytotoxic T cells for nasopharyngeal carcinoma. *Int J Cancer*. 2001;94(1):73–80.
131. Lin CL, Lo WF, Lee TH, et al. Immunization with Epstein-Barr Virus (EBV) peptide-pulsed dendritic cells induces functional CD8+ T-cell immunity and may lead to tumor regression in patients with EBV-positive nasopharyngeal carcinoma. *Cancer Res*. 2002;62(23):6952–6958.
132. Straathof KC, Bollard CM, Popat U, et al. Treatment of nasopharyngeal carcinoma with Epstein-Barr virus-specific T lymphocytes. *Blood*. 2005;105(5):1898–1904.

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